WEST Search History

DATE: Sunday, July 27, 2003

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ			
L12	antiport with modulator	3	L12
L11	antiport near modulator	1	L11
DB=; PLUR=YES; OP=ADJ			
L10	l5 and L9	59	L10
L9	timolol	2181	L9
L8	l3 and l6	1	L8
L7	l5 and L6	1	L7
L6	cariporide	31	L6
L5	l3 and L4	263	L5
L4	l1 or l2	32589	L4
L3	glaucoma	12202	L3
L2	sodium with exchange$2	26546	L2
DB=USPT,PGPB; PLUR=YES; OP=ADJ			
L1	chloride with exchange$2	10576	L1

END OF SEARCH HISTORY

Viprinex (ancrod)	(III)	Knoll	stroke

		associated with ESRD
HOE 901 (insulin glargine) (III)	HMR	types 1 and 2 diabetes
nerve growth factor (III)	Genentech	diabetic peripheral neuropathy
Pimagedine (aminoguanidine) (III)	Alteon	diabetes, ESRD
pramlintide (III)	Amylin	diabetes
zopolrestat (III)	Pfizer	diabetic neuropathy
Starlix (nateglinide) (III)	Novartis	glaucoma
Cynt (moxonidine) (III)	Lilly/Solvay	hypertension
HOE 642A (cariporide) (III)	HMR	acute coronary syndrome
lanoteplase (III)	BMS	acute myocardial infarction
Micardis (telmisartan) (AS)	Boeh Ingelheim	hypertension
omapatrilat (III)	BMS	hypertension
Teveten (eprosartan) (IV)	SB/Int'l Society on Hypertension in Blacks	hypertension
TNK (2nd generation TPA) (III)	Genentech	acute MI
Ariflo (DPE IV inhibitor) (III)	SB	COPD
FluMist (live attenuated intranasal flu vaccine) (AS)	Aviron	influenza
Foradil (formoterol mumaratae powder for inhalation) (AS)	Novartis	asthma, COPD
neuraminidase inhibitor (III)	Roche	influenza
Oxsodrol (superoxide dismutase) (III)	BioTechnology General	prevention of bronchopulmonary dysplasia in premature infants
Relenza (zanamivir) (III)	Glaxo Wellcome	influenza
Surfaxin (lucinactant) (III)	Discovery Laboratories	acute respiratory distress syndrome in adults
Synercid (quinupristin/ dalfopristin) (AS)	RPR	nosocomial pneumonia
Tequin (gatifloxacin) (III)	BMS	pneumonia
Cordox (fructose-1,6 diphosphate) (III)	Cypros	sickle cell disease
Flocor (poloxamer 188, purified) (III)	CytRx	sickle cell disease
CerAxon (citicoline) (III)	Interneuron	stroke
GV150526 (III)	Glaxo Wellcome	stroke

been elucidated. We have studied continuously cultured bovine PE cells. Acid-activated 22Na+ uptake was inhibited by **cariporide**, EIPA (ethyl-isopropyl-amiloride) and amiloride, at concentrations characteristic of the NHE-1 isoform. Videomicroscopy of BCECF-loaded PE cells verified the presence of. . .

IT . . .
of Organisms
aqueous humor: sensory system; ciliary epithelium: sensory system; gap junctions; pigmented ciliary epithelial cell: sensory system

IT Diseases
glaucoma: eye disease

IT Chemicals & Biochemicals
chloride ion hydrogen bicarbonate antiporters; chloride ions; sodium ion: uptake; sodium ion hydrogen ion antiporters

IT Alternate Indexing
Glaucoma (MeSH)

L37 ANSWER 4 OF 4 PHIN COPYRIGHT 2003 PJB on STN

ACCESSION NUMBER: 1998:15688 PHIN
DOCUMENT NUMBER: S00593210
DATA ENTRY DATE: 27 Aug 1998
TITLE: 156 drugs for African-Americans studied
SOURCE: Scrip-Online-plus (1998)
DOCUMENT TYPE: Newsletter
FILE SEGMENT: FULL

TX This . . . such as asthma; 27 for heart disease/hypertension; 18 for HIV infection; 16 for diabetes; nine for stroke; five each for **glaucoma** and sickle cell disease; and four for end-stage renal disease (ESRD).

TX **Glaucoma** occurs six to eight times more often among African-Americans than whites, and it occurs earlier - by age 70, one in ten has **glaucoma**, compared with one in 50 whites.

TX

Product (status)	Company	Indication
abacavir (II/III)	Glaxo Wellcome	HIV infection
amprenavir (III)	Glaxo Wellcome	HIV infection Preveon
(II/III) (adefovir dipivoxil)	Gilead Sciences	HIV infection
Provir (III)	Shaman	HIV infection
valganciclovir (III)	Roche	HIV infection
AG3340 (II/III)	Agouron	prostate cancer
dendritic cell therapy (II/III)	Dendreon	prostate cancer
Eloxatin (III) (oxaliplatin)	Sanofi	liver, pancreatic cancer
eniluracil (II/III)	Glaxo Wellcome	pancreatic cancer
exisulind/FGN-1 (II/III)	Cell Pathways	prevention of recurrence after prostatectomy
Lutrin (photodynamic therapy) (II/III)	Pharmacyclics	pancreatic, prostate cancers
Maxamine (histamine dihydrochloride) (III)	Maxim	multiple myeloma, prostate cancer
Mitalactol (III)	Biopharmaceutics	cervical cancer
satraplatin (III)	BMS	prostate cancer
Avandi (III)	SmithKline Beecham	diabetes
Avapro (irbesartan) (III/AS)	BMS	diabetic neuropathy, ESRD, hypertension
Hectoral (1-alpha-hydroxy vitamin D2) (AS)	Bone Care Int'l	secondary hyperpara-thyroidism

cariporide, particularly in combination with bumetanide to simultaneously block the symport.

DETD . . . A therapeutically effective amount of the combined agent is that amount necessary to significantly reduce or eliminate symptoms associated with **glaucoma**, particularly to reduce or prevent elevated IOP more effectively that the effect of one of the compositions alone would have.. . .

L37 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:814312 CAPLUS
DOCUMENT NUMBER: 133:344642
TITLE: Methods using antiport modulators for controlling intraocular pressure
INVENTOR(S): Civan, Mortimer M.; MacKnight, Anthony D.
PATENT ASSIGNEE(S): The Trustees of the University of Pennsylvania, USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000067756	A1	20001116	WO 2000-US12551	20000508

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-133180P P 19990507
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ST intraocular pressure **glaucoma** treatment antiport modulator; sodium proton exchanger modulation intraocular pressure; chloride bicarbonate exchanger modulation intraocular pressure

IT 100-88-9, Cyclamate 1154-25-2 1214-79-5, Dimethylamiloride 2609-46-3, Amiloride 2609-46-3D, Amiloride, analogs 26839-75-8, Timolol **159138-80-4**, **Cariporide**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiport modulators for controlling intraocular pressure)

L37 ANSWER 3 OF 4 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 1
ACCESSION NUMBER: 2000:449189 BIOSIS
DOCUMENT NUMBER: PREV200000449189
TITLE: Na+/H+ and Cl-/HCO3--antiporters of bovine pigmented ciliary epithelial cells.
AUTHOR(S): Counillon, L.; Touret, Nicolas; Bidet, Michel; Peterson-Yantorno, K.; Coca-Prados, M.; Stuart-Tilley, Alan; Wilhelm, Sabine; Alper, S. L.; Civan, M. M. (1)
CORPORATE SOURCE: (1) Depts. of Physiology and Medicine, University of Pennsylvania, A303 Richards Building, Philadelphia, PA, 19104-6085 USA
SOURCE: Pfluegers Archiv European Journal of Physiology, (September, 2000) Vol. 440, No. 5, pp. 667-678. print.
ISSN: 0031-6768.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Medical therapy of **glaucoma** commonly aims at slowing aqueous humor formation by the ocular ciliary epithelial bilayer, but underlying mechanisms are poorly understood. The. . . paired antiporters have not

```
=> s timolol/cn
L1            1 TIMOLOL/CN

=> d l1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   26839-75-8  REGISTRY
CN   2-Propanol, 1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-
     thiadiazol-3-yl]oxy]-, (2S)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   1,2,5-Thiadiazole, 2-propanol deriv.
CN   2-Propanol, 1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-
     yl)oxy]-, (S)-(-)- (8CI)
CN   2-Propanol, 1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-
     thiadiazol-3-yl]oxy]-, (S)-
OTHER NAMES:
CN   (-)-S-Timolol
CN   (-)-Timolol
CN   (S)-Timolol
CN   l-Timolol
CN   L-Timolol
CN   Oftensin
CN   Timolol
FS   STEREOSEARCH
DR   131628-37-0, 194288-09-0
MF   C13 H24 N4 O3 S
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
       BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMLIST, CIN, CSCHEM,
       DDFU, DIOGENES, DRUGPAT, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB,
       IPA, MEDLINE, MRCK*, NIOSHTIC, PHAR, PHARMASEARCH, PROMT, SPECINFO,
       TOXCENTER, USPAT2, USPATFULL, VETU
         (*File contains numerically searchable property data)
     Other Sources:   EINECS**, NDSL**, TSCA**, WHO
         (**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.  Rotation (-).
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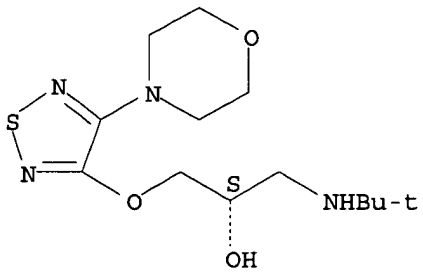


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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

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              19 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
            1164 REFERENCES IN FILE CAPLUS (1947 TO DATE)


=> s amiloride/cn
L2            1 AMILORIDE/CN

=> d l2

L2   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   2609-46-3  REGISTRY
CN   Pyrazinecarboxamide, 3,5-diamino-N-(aminoiminomethyl)-6-chloro- (9CI)  (CA
     INDEX NAME)
OTHER CA INDEX NAMES:
```
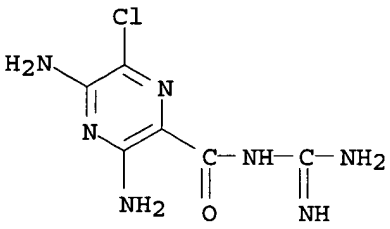

CN Pyrazinecarboxamide, N-amidino-3,5-diamino-6-chloro- (7CI, 8CI)
OTHER NAMES:
CN (3,5-Diamino-6-chloropyrazinoyl)guanidine
CN **Amiloride**
CN Amipramidin
CN Guanamprazine
CN MK 870
CN N-Amidino-3,5-diamino-6-chloropyrazinecarboxamide
FS 3D CONCORD
DR 137053-85-1
MF C6 H8 Cl N7 O
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGPAT, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, NIOSHTIC, PHAR, PROMT, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

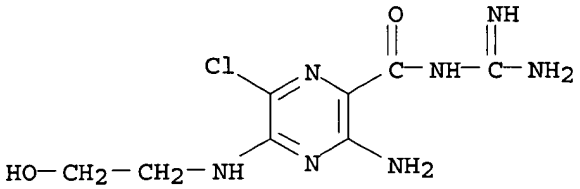


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1952 REFERENCES IN FILE CA (1947 TO DATE)
109 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1957 REFERENCES IN FILE CAPLUS (1947 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

```
=> s ethyl isopropyl amiloride
       5535816 ETHYL
         84162 ISOPROPYL
           131 AMILORIDE
L3           0 ETHYL ISOPROPYL AMILORIDE
                 (ETHYL(W)ISOPROPYL(W)AMILORIDE)

=> s isopropyl ethyl amiloride
         84162 ISOPROPYL
       5535816 ETHYL
           131 AMILORIDE
L4           0 ISOPROPYL ETHYL AMILORIDE
                 (ISOPROPYL(W)ETHYL(W)AMILORIDE)

=> s amiloride
L5         131 AMILORIDE

=> s ethyl amiloride
       5535816 ETHYL
           131 AMILORIDE
L6           4 ETHYL AMILORIDE
                 (ETHYL(W)AMILORIDE)

=> d l6 1-4

L6   ANSWER 1 OF 4  REGISTRY  COPYRIGHT 2003 ACS on STN
```

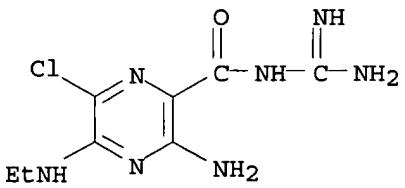
RN 67879-54-3 REGISTRY
CN Pyrazinecarboxamide, 3-amino-N-(aminoiminomethyl)-6-chloro-5-[(2-hydroxyethyl)amino]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **5-[N-(2-Hydroxyethyl)]amiloride**
FS 3D CONCORD
MF C8 H12 Cl N7 O2
CI COM
LC STN Files: BEILSTEIN*, CA, CAPLUS
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1947 TO DATE)
2 REFERENCES IN FILE CAPLUS (1947 TO DATE)

L6 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2003 ACS on STN
RN 2235-96-3 REGISTRY
CN Pyrazinecarboxamide, 3-amino-N-(aminoiminomethyl)-6-chloro-5-(ethylamino)-(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Pyrazinecarboxamide, N-amidino-3-amino-6-chloro-5-(ethylamino)- (7CI, 8CI)
OTHER NAMES:
CN **5-(N-Ethyl)amiloride**
FS 3D CONCORD
MF C8 H12 Cl N7 O
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, IFICDB, IFIPAT, IFIUDB, SPECINFO
(*File contains numerically searchable property data)

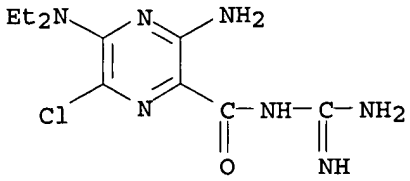


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

11 REFERENCES IN FILE CA (1947 TO DATE)
11 REFERENCES IN FILE CAPLUS (1947 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L6 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2003 ACS on STN
RN 2086-31-9 REGISTRY
CN Pyrazinecarboxamide, 3-amino-N-(aminoiminomethyl)-6-chloro-5-(diethylamino)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Pyrazinecarboxamide, N-amidino-3-amino-6-chloro-5-(diethylamino)- (7CI, 8CI)
OTHER NAMES:
CN **5-(N,N-Diethyl)amiloride**
FS 3D CONCORD
MF C10 H16 Cl N7 O

CI COM
LC STN Files: BEILSTEIN*, CA, CANCERLIT, CAOLD, CAPLUS, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE
(*File contains numerically searchable property data)



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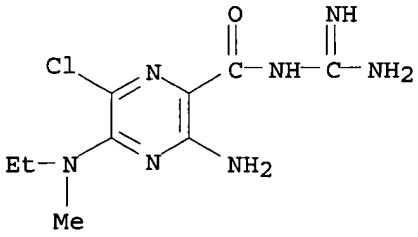
12 REFERENCES IN FILE CAPLUS (1947 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L6 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2003 ACS on STN
RN 1148-33-0 REGISTRY
CN Pyrazinecarboxamide, 3-amino-N-(aminoiminomethyl)-6-chloro-5-(ethylmethylamino)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Pyrazinecarboxamide, N-amidino-3-amino-6-chloro-5-(ethylmethylamino)-(7CI, 8CI)
OTHER NAMES:
CN **5-(N-Methyl-N-ethyl)amiloride**
FS 3D CONCORD
MF C9 H14 Cl N7 O
CI COM
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, IFICDB, IFIPAT, IFIUDB
(*File contains numerically searchable property data)



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17 REFERENCES IN FILE CAPLUS (1947 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> s cariporide/cn
L7 1 CARIPORIDE/CN

=> d l7

L7 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN 159138-80-4 REGISTRY
CN Benzamide, N-(aminoiminomethyl)-4-(1-methylethyl)-3-(methylsulfonyl)-(9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Cariporide**
FS 3D CONCORD
MF C12 H17 N3 O3 S
CI COM

SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CBNB, CIN, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MRCK*, PHAR, PROMT, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
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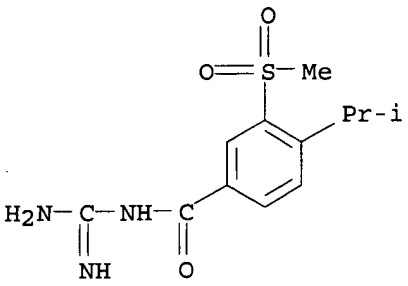

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=> file medicine
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=>

=> d his

     (FILE 'HOME' ENTERED AT 18:29:32 ON 27 JUL 2003)

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L2             1 S AMILORIDE/CN
L3             0 S ETHYL ISOPROPYL AMILORIDE
L4             0 S ISOPROPYL ETHYL AMILORIDE
L5           131 S AMILORIDE
L6             4 S ETHYL AMILORIDE
L7             1 S CARIPORIDE/CN

     FILE 'ADISCTI, ADISINSIGHT, ADISNEWS, BIOSIS, CANCERLIT, CAPLUS, CEN,
     DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL, EMBASE,
     ESBIOBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDICONF, MEDLINE,
     NAPRALERT, NLDB, NUTRACEUT, PASCAL, PCTGEN, ...' ENTERED AT 18:33:21 ON
     27 JUL 2003

=> s l1 or timolol
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L8         31558 L1 OR TIMOLOL

=> s l2 or amiloride

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L9         64288 L2 OR AMILORIDE

=> s l7 or acriporide

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L10 507 L7 OR ACRIPORIDE

=> s l7 or cariporide
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L11 1505 L7 OR CARIPORIDE

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(FILE 'HOME' ENTERED AT 18:29:32 ON 27 JUL 2003)

FILE 'REGISTRY' ENTERED AT 18:29:44 ON 27 JUL 2003
L1 1 S TIMOLOL/CN
L2 1 S AMILORIDE/CN
L3 0 S ETHYL ISOPROPYL AMILORIDE
L4 0 S ISOPROPYL ETHYL AMILORIDE
L5 131 S AMILORIDE
L6 4 S ETHYL AMILORIDE
L7 1 S CARIPORIDE/CN

FILE 'ADISCTI, ADISINSIGHT, ADISNEWS, BIOSIS, CANCERLIT, CAPLUS, CEN, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL, EMBASE, ESBIOBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDICONF, MEDLINE, NAPRALERT, NLDB, NUTRACEUT, PASCAL, PCTGEN, ...' ENTERED AT 18:33:21 ON 27 JUL 2003
L8 31558 S L1 OR TIMOLOL
L9 64288 S L2 OR AMILORIDE
L10 507 S L7 OR ACRIPORIDE
L11 1505 S L7 OR CARIPORIDE

=> s l8 or l9 or l11
L12 95722 L8 OR L9 OR L11

=> s glaucoma
L13 159500 GLAUCOMA

=> s aqueous humor
L14 34931 AQUEOUS HUMOR

=> s s antiport (s) modulat?
23 FILES SEARCHED...
L15 0 S ANTIPORT (S) MODULAT?

=> s antiport (s) modulat?
L16 457 ANTIPORT (S) MODULAT?

=> s antiport? (s) modulat?
L17 923 ANTIPORT? (S) MODULAT?

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L18       9965 L12 AND L13

=> s l18 and l17
L19         13 L18 AND L17

=> dup rem
ENTER L# LIST OR (END):l19
DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, DGENE, DRUGLAUNCH,
DRUGMONOG2, KOSMET, MEDICONF, NUTRACEUT, PCTGEN, PHARMAML'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L19
L20          10 DUP REM L19 (3 DUPLICATES REMOVED)

=> d l20 1-10 ibib, kwic

L20  ANSWER 1 OF 10  CAPLUS  COPYRIGHT 2003 ACS on STN DUPLICATE 1
ACCESSION NUMBER:         2003:334635  CAPLUS
DOCUMENT NUMBER:          138:331729
TITLE:                    Novel combination therapy to treat glaucoma
INVENTOR(S):              Civan, Mortimer M.; Jacobson, Kenneth A.; MacKnight,
                          Anthony D. C.; Mitchell, Claire H.; Stone, Richard A.
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 19 pp., Cont.-in-part of U. S.
                          Ser. No. 9,581.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.   DATE
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     US 2003083227      A1   20030501       US 2002-217755    20020813
PRIORITY APPLN. INFO.:                   US 1999-133180P   P  19990507
                                         US 2001-312036P   P  20010813
                                         US 2002-9581      A2 20020430
TI   Novel combination therapy to treat glaucoma
ST   glaucoma treatment modulation aq humor secretion; biol transport
     modulation aq humor glaucoma; sodium hydrogen exchanger
     inhibition glaucoma treatment; chloride channel inhibition aq
     humor formation; bumetanide dimethylamiloride dorzolamide intraocular
     pressure redn
IT   Purinoceptor antagonists
        (A3; combination therapy to treat glaucoma by controlling
        secretion of excess fluids into aq. humor)
IT   Adenosine receptors
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (A3, lower intraocular pressure in mice lacking gene for; combination
        therapy to treat glaucoma by controlling secretion of excess
        fluids into aq. humor)
IT   Biological transport
        (antiport, modulator of; combination therapy to
        treat glaucoma by controlling secretion of excess fluids into
        aq. humor)
IT   Eye
        (aq. humor; combination therapy to treat glaucoma by
        controlling secretion of excess fluids into aq. humor)
IT   Transport proteins
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (bicarbonate-chloride-exchanging, AE2, modulator of; combination
        therapy to treat glaucoma by controlling secretion of excess
        fluids into aq. humor)
IT   Transport proteins
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (bicarbonate-chloride-exchanging, modulator of; combination therapy to
        treat glaucoma by controlling secretion of excess fluids into
        aq. humor)
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IT Transport proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(chloride-potassium-sodium cotransporter, modulator of; combination therapy to treat **glaucoma** by controlling secretion of excess fluids into aq. humor)
IT Ion channel blockers
(chloride; combination therapy to treat **glaucoma** by controlling secretion of excess fluids into aq. humor)
IT Eye
(ciliary epithelium; combination therapy to treat **glaucoma** by controlling secretion of excess fluids into aq. humor)
IT Antiglaucoma agents
Glaucoma (disease)
Mouse
(combination therapy to treat **glaucoma** by controlling secretion of excess fluids into aq. humor)
IT Biological transport
(cotransport, modulator of; combination therapy to treat **glaucoma** by controlling secretion of excess fluids into aq. humor)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(for A3 adenosine receptor, lower intraocular pressure in mice lacking; combination therapy to treat **glaucoma** by controlling secretion of excess fluids into aq. humor)
IT Transport proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hydrogen ion-sodium-exchanging, NHE-1, modulator of; combination therapy to treat **glaucoma** by controlling secretion of excess fluids into aq. humor)
IT Transport proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hydrogen ion-sodium-exchanging, modulator of; combination therapy to treat **glaucoma** by controlling secretion of excess fluids into aq. humor)
IT Eye
(intraocular fluid; combination therapy to treat **glaucoma** by controlling secretion of excess fluids into aq. humor)
IT Drug interactions
(synergistic; combination therapy to treat **glaucoma** by controlling secretion of excess fluids into aq. humor)
IT 120279-96-1, Dorzolamide
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carbonic anhydrase inhibitor; combination therapy to treat **glaucoma** by controlling secretion of excess fluids into aq. humor)
IT 53005-05-3, 4,4'-Diisothiocyanatostilbene-2,2'-disulfonic acid
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chloride-bicarbonate-exchanger blocker; combination therapy to treat **glaucoma** by controlling secretion of excess fluids into aq. humor)
IT 28395-03-1, Bumetanide
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chloride-potassium-sodium cotransporter blocker; combination therapy to treat **glaucoma** by controlling secretion of excess fluids into aq. humor)
IT **2609-46-3, Amiloride**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(combination therapy to treat **glaucoma** by controlling secretion of excess fluids into aq. humor)
IT 59-66-5, Acetazolamide
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy to treat **glaucoma** by controlling secretion of excess fluids into aq. humor)
IT 9001-03-0, Carbonic anhydrase

RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitor; combination therapy to treat **glaucoma** by controlling secretion of excess fluids into aq. humor)

IT 1154-25-2 1214-79-5, Dimethylamiloride 517874-58-7, BIIB 723
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sodium-hydrogen ion antiport blocker; combination therapy to treat **glaucoma** by controlling secretion of excess fluids into aq. humor)

L20 ANSWER 2 OF 10 USPATFULL DUPLICATE on STN2
ACCESSION NUMBER: 2003:3060 USPATFULL
TITLE: Anti-angiogenic compositions and methods of use
INVENTOR(S): Hunter, William L., Vancouver, CANADA
Machan, Lindsay S., Vancouver, CANADA
Arsenault, A. Larry, Paris, CANADA

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003003094	A1	20030102
	US 6544544	B2	20030408
APPLICATION INFO.:	US 2001-925220	A1	20010808 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-294458, filed on 19 Apr 1999, PENDING Continuation of Ser. No. US 1995-480260, filed on 7 Jun 1995, ABANDONED Division of Ser. No. US 1995-417160, filed on 3 Apr 1995, ABANDONED Continuation-in-part of Ser. No. US 1993-94536, filed on 19 Jul 1993, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	WO 1994-CA373	19940719

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 75 Drawing Page(s)
LINE COUNT: 5049
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . for example: .alpha.-adrenergic blocking agents, angiotensin II receptor antagonists and receptor antagonists for histamine, serotonin, endothelin; inhibitors of the sodium/hydrogen **antiporter** (e.g., **amiloride** and its derivatives); agents that **modulate** intracellular Ca.sup.2+ transport such as L-type (e.g., diltiazem, nifedipine, verapamil) or T-type Ca.sup.2+ channel blockers (e.g., **amiloride**), calmodulin antagonists (e.g., H7) and inhibitors of the sodium/calcium **antiporter** (e.g., **amiloride**); ap-1 inhibitors (for tyrosine kinases, protein kinase C, myosin light chain kinase, Ca.sup.2+/calmodulin kinase 11, casein kinase II); anti-depressants (e.g.. . .

DETD . . . above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular **glaucoma**, proliferative diabetic retinopathy, retrolental fibroblasia and macular degeneration.

DETD [0232] Within another aspect of the present invention, methods are provided for treating neovascular **glaucoma**, comprising the step of administering to a patient a therapeutically effective amount of an anti-angiogenic composition to the eye, such. . .

DETD [0233] Briefly, neovascular **glaucoma** is a pathological condition wherein new capillaries develop in the iris of the eye. The angiogenesis usually originates from vessels. . .

DETD [0234] Neovascular **glaucoma** generally occurs as a complication of diseases in which retinal ischemia is predominant. In particular. about one third of the. . . with this disorder have diabetic retinopathy and 28% have central retinal vein occlusion. Other causes include chronic retinal detachment, end-stage **glaucoma**,

carotid artery obstructive disease, retrolental fibroplasia, sickle-cell anemia, intraocular tumors, and carotid cavernous fistulas. In its early stages, neovascular **glaucoma** may be diagnosed by high magnification slitlamp biomicroscopy, where it reveals small, dilated, disorganized capillaries (which leak fluorescein) on the. . .

DETD . . . anti-angiogenic composition, as described above) may be administered topically to the eye in order to treat early forms of neovascular **glaucoma**.

DETD [0238] Briefly, the pathology of diabetic retinopathy is thought to be similar to that described above for neovascular **glaucoma**. In particular, background diabetic retinopathy is believed to convert to proliferative diabetic retinopathy under the influence of retinal hypoxia. Generally,. . .

DETD . . . a decrease in peripheral vision of up to 50% of patients, mechanical abrasions of the cornea, laser-induced cataract formation, acute **glaucoma**, and stimulation of subretinal neovascular growth (which can result in loss of vision). As a result, this procedure is performed. . .

DETD . . . the vessels and the retina This results in vitreous hemorrhage and/or retinal detachment which can lead to blindness. Neovascular angle-closure **glaucoma** is also a complication of this condition.

L20 ANSWER 3 OF 10 USPATFULL on STN

ACCESSION NUMBER:	2003:4168 USPATFULL
TITLE:	Anti-angiogenic compositions and methods of use
INVENTOR(S):	Hunter, William L., Vancouver, CANADA Machan, Lindsay S., Vancouver, CANADA Arsenault, A. Larry, Paris, CANADA
PATENT ASSIGNEE(S):	Angiotech Pharmaceuticals, Inc., Vancouver, BC, CANADA, V6T 1Z4 (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003004209	A1	20030102
APPLICATION INFO.:	US 2002-112921	A1	20020328 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1998-13765, filed on 27 Jan 1998, ABANDONED Continuation of Ser. No. US 1995-478914, filed on 7 Jun 1995, GRANTED, Pat. No. US 5994341 Division of Ser. No. US 1995-417160, filed on 3 Apr 1995, ABANDONED Continuation-in-part of Ser. No. US 1993-94536, filed on 19 Jul 1993, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	WO 1994-CA373	19940719

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092
NUMBER OF CLAIMS:	61
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	76 Drawing Page(s)
LINE COUNT:	5230

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . for example: .alpha.-adrenergic blocking agents, angiotensin II receptor antagonists and receptor antagonists for histamine, serotonin, endothelin; inhibitors of the sodium/hydrogen **antiporter** (e.g., **amiloride** and its derivatives); agents that **modulate** intracellular Ca.sup.2+transport such as L-type (e.g., diltiazem, nifedipine, verapamil) or T-type Ca.sup.2+channel blockers (e.g., **amiloride**), calmodulin antagonists (e.g., H.sub.7) and inhibitors of the sodium/calcium **antiporter** (e.g., **amiloride**); ap-1 inhibitors (for tyrosine kinases, protein kinase C, myosin light chain kinase, Ca.sup.2+/calmodulin kinase II, casein kinase II); anti-depressants (e.g.. . .

DETD . . . above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular **glaucoma**, proliferative

diabetic retinopathy, retrolental fibroblasia and macular degeneration.

DETD . . . reduce inflammation resulting from the injection itself Within another aspect of the present invention, methods are provided for treating neovascular **glaucoma**, comprising the step of administering to a patient a therapeutically effective amount of an anti-angiogenic composition to the eye, such. . .

DETD [0194] Briefly, neovascular **glaucoma** is a pathological condition wherein new capillaries develop in the iris of the eye. The angiogenesis usually originates from vessels. . .

DETD [0195] Neovascular **glaucoma** generally occurs as a complication of diseases in which retinal ischemia is predominant. In particular, about one third of the. . . with this disorder have diabetic retinopathy and 28% have central retinal vein occlusion. Other causes include chronic retinal detachment, end-stage **glaucoma**, carotid artery obstructive disease, retrolental fibroplasia, sickle-cell anemia, intraocular tumors, and carotid cavernous fistulas. In its early stages, neovascular **glaucoma** may be diagnosed by high magnification slitlamp biomicroscopy, where it reveals small, dilated, disorganized capillaries (which leak fluorescein) on the. . .

DETD . . . anti-angiogenic composition, as described above) may be administered topically to the eye in order to treat early forms of neovascular **glaucoma**.

DETD [0199] Briefly, the pathology of diabetic retinopathy is thought to be similar to that described above for neovascular **glaucoma**. In particular, background diabetic retinopathy is believed to convert to proliferative diabetic retinopathy under the influence of retinal hypoxia. Generally,. . .

DETD . . . a decrease in peripheral vision of up to 50% of patients, mechanical abrasions of the cornea, laser-induced cataract formation, acute **glaucoma**, and stimulation of subretinal neovascular growth (which can result in loss of vision). As a result, this procedure is performed. . .

DETD . . . the vessels and the retina. This results in vitreous hemorrhage and/or retinal detachment which can lead to blindness. Neovascular angle-closure **glaucoma** is also a complication of this condition.

L20 ANSWER 4 OF 10 USPATFULL DUPLICATE on STN3

ACCESSION NUMBER: 2002:294335 USPATFULL
TITLE: ANTI-ANGIOGENIC COMPOSITIONS AND METHODS OF USE
INVENTOR(S): HUNTER, WILLIAM L, BRITISH COLUMBIA, CANADA
MACHAN, LINDSAY S, BRITISH COLUMBIA, CANADA
ARSENAULT, A LARRY, ONTARIO, CANADA

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002164377	A1	20021107
	US 6506411	B2	20030114
APPLICATION INFO.:	US 1999-294458	A1	19990419 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1995-480260, filed on 7 Jun 1995, ABANDONED Division of Ser. No. US 1995-417160, filed on 3 Apr 1995, ABANDONED Division of Ser. No. US 1993-94536, filed on 19 Jul 1993, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	WO 1994-CA373	19940719

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092
NUMBER OF CLAIMS: 61
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 82 Drawing Page(s)
LINE COUNT: 5243
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . for example: .alpha.-adrenergic blocking agents, angiotensin II receptor antagonists and receptor antagonists for histamine, serotonin, endothelin; inhibitors of the sodium/hydrogen **antiporter**

(e.g., **amiloride** and its derivatives); agents that **modulate** intracellular Ca.sup.2- transport such as L-type (e.g., diltiazem, nifedipine, verapamil) or T-type Ca.sup.2+ channel blockers (e.g., **amiloride**). calmodulin antagonists (e.g., H.sub.7) and inhibitors of the sodium/calcium **antiporter** (e.g., **amiloride**); ap-1 inhibitors (for tyrosine kinases, protein kinase C, myosin light chain kinase, Ca.sup.2+/calmodulin kinase II, casein kinase II); anti-depressants (e.g.. . .

DETD . . . above, the present invention also provides methods for treating neovascular diseases of the eve, including for example, corneal neovascularization, neovascular **glaucoma**, proliferative diabetic retinopathy, retrolental fibroblasia and macular degeneration.

DETD [0233] Within another aspect of the present invention, methods are provided for treating neovascular **glaucoma**, comprising the step of administering to a patient a therapeutically effective amount of an anti-angiogenic composition to the eye, such. . .

DETD [0234] Briefly, neovascular **glaucoma** is a pathological condition wherein new capillaries develop in the iris of the eye. The angiogenesis usually originates, from vessels. . .

DETD [0235] Neovascular **glaucoma** Generally occurs as a complication of diseases in which retinal ischemia is predominant. In particular, about one third of the. . . with this disorder have diabetic retinopathy and 28% have central retinal vein occlusion. Other causes include chronic retinal detachment, end-stage **glaucoma**, carotid artery obstructive disease, retrolental fibroplasia, sickle-cell anemia, intraocular tumors, and carotid cavernous fistulas. In its early stages, neovascular **glaucoma** may be diagnosed by high magnification slitlamp biomicroscopy, where it reveals small, dilated, disorganized capillaries (which leak fluorescein) on the. . .

DETD . . . anti-angiogenic composition, as described above) may be administered topically to the eye in order to treat early forms of neovascular **glaucoma**.

DETD [0239] Briefly, the pathology of diabetic retinopathy is thought to be similar to that described above for neovascular **glaucoma**. In particular, background diabetic retinopathy is believed to convert to proliferative diabetic retinopathy under the influence of retinal hypoxia. Generally,. . .

DETD . . . a decrease in peripheral vision of up to 50% of patients, mechanical abrasions of the cornea, laser-induced cataract formation, acute **glaucoma**, and stimulation of subretinal neovascular growth (which can result in loss of vision). As a result, this procedure is performed. . .

DETD . . . the vessels and the retina. This results in vitreous hemorrhage and/or retinal detachment which can lead to blindness. Neovascular angle-closure **glaucoma** is also a complication of this condition

L20 ANSWER 5 OF 10 USPATFULL on STN

ACCESSION NUMBER:	2002:295216 USPATFULL
TITLE:	ANTI-ANGIOGENIC COMPOSITIONS AND METHODS OF USE
INVENTOR(S):	HUNTER, WILLIAM L., VANCOUVER, CANADA MACHAN, LINDSAY S., VANCOUVER, CANADA ARSENAULT, A. LARRY, PARIS ON, CANADA

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002165265	A1	20021107
APPLICATION INFO.:	US 1997-984258	A1	19971203 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1995-478203, filed on 7 Jun 1995, GRANTED, Pat. No. US 5716981 Division of Ser. No. US 1995-417160, filed on 3 Apr 1995, ABANDONED Continuation-in-part of Ser. No. US 1993-94536, filed on 19 Jul 1993, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	WO 1994-CA373	19940719

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION

LEGAL REPRESENTATIVE: SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092
NUMBER OF CLAIMS: 61
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 82 Drawing Page(s)
LINE COUNT: 5231
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . for example: .alpha.-adrenergic blocking agents, angiotensin II receptor antagonists and receptor antagonists for histamine. serotonin, endothelin; inhibitors of the sodium/hydrogen **antiporter** (e.g., **amiloride** and its derivatives); agents that **modulate** intracellular Ca.sup.2+ transport such as L-type (e.g. diltiazem, nifedipine, verapamil) or T-type Ca.sup.2+ channel blockers (e.g., **amiloride**), calmodulin antagonists (e.g., H.sub.7) and inhibitors of the sodium/calcium **antiporter** (e.g., **amiloride**); ap-1 inhibitors (for tyrosine kinases, protein kinase C. myosin light chain kinase. Ca.sup.2+/calmodulin kinase II, casein kinase II); anti-depressants (e.g.. . .

DETD . . . above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular **glaucoma**, proliferative diabetic retinopathy, retrolental fibroblasia and macular degeneration.

DETD [0194] Within another aspect of the present invention, methods are provided for treating neovascular **glaucoma**, comprising the step of administering to a patient a therapeutically effective amount of an anti-angiogenic composition to the eye, such. . .

DETD [0195] Briefly, neovascular **glaucoma** is a pathological condition wherein new capillaries develop in the iris of the eye. The angiogenesis usually originates from vessels. . .

DETD [0196] Neovascular **glaucoma** generally occurs as a complication of diseases in which retinal ischemia is predominant. In particular, about one third of the. . . with this disorder have diabetic retinopathy and 28% have central retinal vein occlusion. Other causes include chronic retinal detachment, end-stage **glaucoma**, carotid artery obstructive disease, retrolental fibroplasia, sickle-cell anemia. intraocular tumors, and carotid cavernous fistulas. In its early stages, neovascular **glaucoma** may be diagnosed by high magnification slitlamp biomicroscopy, where it reveals small, dilated, disorganized capillaries (which leak fluorescein) on the. . .

DETD . . . anti-angiogenic composition, as described above) may be administered topically to the eye in order to treat early forms of neovascular **glaucoma**.

DETD [0200] Briefly, the pathology of diabetic retinopathy is thought to be similar to that described above for neovascular **glaucoma**. In particular, background diabetic retinopathy is believed to convert to proliferative diabetic retinopathy under the influence of retinal hypoxia. Generally,. . .

DETD . . . a decrease in peripheral vision of up to 50% of patients, mechanical abrasions of the cornea, laser-induced cataract formation, acute **glaucoma**, and stimulation of subretinal neovascular growth (which can result in loss of vision). As a result, this procedure is performed. . .

DETD . . . the vessels and the retina. This results in vitreous hemorrhage and/or retinal detachment which can lead to blindness. Neovascular angle-closure **glaucoma** is also a complication of this condition

L20 ANSWER 6 OF 10 USPATFULL on STN
ACCESSION NUMBER: 2002:221067 USPATFULL
TITLE: Anti-angiogenic compositions and methods of use
INVENTOR(S): Hunter, William L., Vancouver, CANADA
Machan, Lindsay S., Vancouver, CANADA
Arsenault, A. Larry, Paris, CANADA
Burt, Helen M., Vancouver, CANADA
Jackson, John K., Vancouver, CANADA
Dordunoo, Stephen K., Vancouver, CANADA

NUMBER	KIND	DATE

PATENT INFORMATION: US 2002119202 A1 20020829
APPLICATION INFO.: US 2001-927882 A1 20010809 (9)
RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-294458, filed on 19 Apr 1999, PENDING Continuation of Ser. No. US 1995-480260, filed on 7 Jun 1995, ABANDONED Division of Ser. No. US 1995-417160, filed on 3 Apr 1995, ABANDONED Division of Ser. No. US 1993-94536, filed on 19 Jul 1993, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	WO 1994-CA373	19940719

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SEED INTELLECTUAL PROPERTY LAW GROUP PLLC, 701 FIFTH AVE, SUITE 6300, SEATTLE, WA, 98104-7092
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 75 Drawing Page(s)
LINE COUNT: 5037
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . for example: .alpha.-adrenergic blocking agents, angiotensin II receptor antagonists and receptor antagonists for histamine, serotonin, endothelin; inhibitors of the sodium/hydrogen **antiporter** (e.g., **amiloride** and its derivatives); agents that **modulate** intracellular Ca.sup.2+ transport such as L-type (e.g., diltiazem, nifedipine, verapamil) or T-type Ca.sup.2+ channel blockers (e.g., **amiloride**), calmodulin antagonists (e.g., H.sub.7) and inhibitors of the sodium/calcium **antiporter** (e.g., **amiloride**); ap-1 inhibitors (for tyrosine kinases, protein kinase C, myosin light chain kinase, Ca.sup.2+/calmodulin kinase II, casein kinase II); anti-depressants (e.g.. . .

DETD . . . above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular **glaucoma**, proliferative diabetic retinopathy, retrolental fibroblasia and macular degeneration.

DETD [0197] Within another aspect of the present invention, methods are provided for treating neovascular **glaucoma**, comprising the step of administering to a patient a therapeutically effective amount of an anti-angiogenic composition to the eye, such. . .

DETD [0198] Briefly, neovascular **glaucoma** is a pathological condition wherein new capillaries develop in the iris of the eye. The angiogenesis usually originates from vessels. . .

DETD [0199] Neovascular **glaucoma** generally occurs as a complication of diseases in which retinal ischemia is predominant. In particular, about one third of the. . . with this disorder have diabetic retinopathy and 28% have central retinal vein occlusion. Other causes include chronic retinal detachment, end-stage **glaucoma**, carotid artery obstructive disease, retrolental fibroplasia, sickle-cell anemia, intraocular tumors, and carotid cavernous fistulas. In its early stages, neovascular **glaucoma** may be diagnosed by high magnification slitlamp biomicroscopy, where it reveals small, dilated, disorganized capillaries (which leak fluorescein) on the. . .

DETD . . . anti-angiogenic composition, as described above) may be administered topically to the eye in order to treat early forms of neovascular **glaucoma**.

DETD [0203] Briefly, the pathology of diabetic retinopathy is thought to be similar to that described above for neovascular **glaucoma**. In particular, background diabetic retinopathy is believed to convert to proliferative diabetic retinopathy under the influence of retinal hypoxia. Generally,. . .

DETD . . . a decrease in peripheral vision of up to 50% of patients, mechanical abrasions of the cornea, laser-induced cataract formation, acute **glaucoma**, and stimulation of subretinal neovascular growth (which can result in loss of vision). As a result, this procedure is performed. . .

DETD . . . the vessels and the retina. This results in vitreous hemorrhage and/or retinal detachment which can lead to blindness. Neovascular angle-closure **glaucoma** is also a complication of this

condition.

L20 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:814312 CAPLUS
DOCUMENT NUMBER: 133:344642
TITLE: Methods using **antiport modulators** for controlling intraocular pressure
INVENTOR(S): Civan, Mortimer M.; MacKnight, Anthony D.
PATENT ASSIGNEE(S): The Trustees of the University of Pennsylvania, USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000067756	A1	20001116	WO 2000-US12551	20000508

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-133180P P 19990507
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Methods using **antiport modulators** for controlling intraocular pressure
ST intraocular pressure **glaucoma** treatment **antiport modulator**; sodium proton exchanger modulation intraocular pressure; chloride bicarbonate exchanger modulation intraocular pressure
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(AE2 **antiport**; **antiport modulators** for controlling intraocular pressure)
IT Adenosine receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(A3; **antiport modulators** for controlling intraocular pressure)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NHE-1 **antiport**; **antiport modulators** for controlling intraocular pressure)
IT Antiglaucoma agents
Secretion (process)
pH
(**antiport modulators** for controlling intraocular pressure)
IT Biological transport
(**antiport**, chloride-bicarbonate; **antiport modulators** for controlling intraocular pressure)
IT Eye
(aq. humor; **antiport modulators** for controlling intraocular pressure)
IT Ion channel blockers
(chloride; **antiport modulators** for controlling intraocular pressure)
IT Eye
(ciliary epithelium, nonpigmented; **antiport modulators** for controlling intraocular pressure)
IT Eye

(ciliary epithelium, pigmented; **antiport modulators** for controlling intraocular pressure)

IT Eye
(ciliary epithelium; **antiport modulators** for controlling intraocular pressure)

IT Drug delivery systems
(ophthalmic; **antiport modulators** for controlling intraocular pressure)

IT Biological transport
(sodium-hydrogen **antiport**; **antiport modulators** for controlling intraocular pressure)

IT Adrenoceptor antagonists
(.beta.-; **antiport modulators** for controlling intraocular pressure)

IT 56-84-8, L-Aspartic acid, biological studies 59-66-5, Acetazolamide 60-92-4, Cyclic AMP 28395-03-1, Bumetanide 53005-05-3, DIDS 149725-40-6, HOE694 152918-18-8, IB-MECA
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**antiport modulators** for controlling intraocular pressure)

IT 100-88-9, Cyclamate 1154-25-2 1214-79-5, Dimethylamiloride **2609-46-3**, **Amiloride 2609-46-3D**, **Amiloride**, analogs **26839-75-8**, **Timolol 159138-80-4**, **Cariporide**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**antiport modulators** for controlling intraocular pressure)

IT 71-52-3, Bicarbonate, biological studies 7440-09-7, Potassium, biological studies 7440-23-5, Sodium, biological studies 12408-02-5, Hydrogen ion, biological studies 16887-00-6, Chloride, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**antiport modulators** for controlling intraocular pressure)

L20 ANSWER 8 OF 10 USPATFULL on STN

ACCESSION NUMBER:	1999:155724 USPATFULL
TITLE:	Anti-angiogenic Compositions and methods for the treatment of arthritis
INVENTOR(S):	Hunter, William L., Vancouver, Canada Machan, Lindsay S., Vancouver, Canada Arsenault, A. Larry, Paris, Canada
PATENT ASSIGNEE(S):	Angiogenesis Technologies, Inc., Vancouver, Canada (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5994341		19991130
APPLICATION INFO.:	US 1995-478914		19950607 (8)
RELATED APPLN. INFO.:	Division of Ser. No. US 1995-417160, filed on 3 Apr 1995, now abandoned which is a continuation-in-part of Ser. No. US 1993-94536, filed on 19 Jul 1993, now abandoned		

	NUMBER	DATE
PRIORITY INFORMATION:	WO 1994-CA373	19940719

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Kumar, Shailendra
LEGAL REPRESENTATIVE:	Seed & Berry LLP
NUMBER OF CLAIMS:	8
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	129 Drawing Figure(s); 75 Drawing Page(s)
LINE COUNT:	5044

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . for example: .alpha.-adrenergic blocking agents, angiotensin II receptor antagonists and receptor antagonists for histamine, serotonin, endothelin; inhibitors of the sodium/hydrogen **antiporter** (e.g., **amiloride** and its derivatives); agents that **modulate** intracellular Ca.sup.2+ transport such as L-type (e.g., diltiazem, nifedipine, verapamil) or T-type Ca.sup.2+ channel blockers (e.g., **amiloride**), calmodulin antagonists (e.g., H.sub.7) and inhibitors of the sodium/calcium **antiporter** (e.g., **amiloride**); ap-1 inhibitors (for tyrosine kinases, protein kinase C, myosin light chain kinase, Ca.sup.2+ /calmodulin kinase II, casein kinease II); anti-depressants. . .

DETD . . . above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular **glaucoma**, proliferative diabetic retinopathy, retrolental fibroblasia and macular degeneration.

DETD Within another aspect of the present invention, methods are provided for treating neovascular **glaucoma**, comprising the step of administering to a patient a therapeutically effective amount of an anti-angiogenic composition to the eye, such. . .

DETD Briefly, neovascular **glaucoma** is a pathological condition wherein new capillaries develop in the iris of the eye. The angiogensis usually originates from vessels. . .

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DETD . . . the vessels and the retina. This results in vitreous hemorrhage and/or retinal detachment which can lead to blindness. Neovascular angle-closure **glaucoma** is also a complication of this condition.

L20 ANSWER 9 OF 10 USPATFULL on STN

ACCESSION NUMBER: 1999:37140 USPATFULL

TITLE: Anti-angiogenic compositions and methods of use

INVENTOR(S): Hunter, William L., Vancouver, Canada
Machan, Lindsay S., Vancouver, Canada
Arsenault, A. Larry, Paris, Canada

PATENT ASSIGNEE(S): Angiotech Pharmaceuticals Inc., Vancouver, Canada (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5886026		19990323
APPLICATION INFO.:	US 1995-472413		19950607 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-417160, filed on 3 Apr 1995, now abandoned which is a continuation-in-part of Ser. No. US 1993-94536, filed on 19 Jul 1993, now abandoned

	NUMBER	DATE
PRIORITY INFORMATION:	WO 1994-CA373	19940719
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	Granted	
PRIMARY EXAMINER:	Kumar, Shailendra	
LEGAL REPRESENTATIVE:	Seed and Berry LLP	
NUMBER OF CLAIMS:	6	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	130 Drawing Figure(s); 75 Drawing Page(s)	
LINE COUNT:	4997	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . for example: .alpha.-adrenergic blocking agents, angiotensin II receptor antagonists and receptor antagonists for histamine, serotonin, endothelin; inhibitors of the sodium/hydrogen **antiporter** (e.g., **amiloride** and its derivatives); agents that **modulate** intracellular Ca.sup.2+ transport such as L-type (e.g., diltiazem, nifedipine, verapamil) or T-type Ca.sup.2+ channel blockers (e.g., **amiloride**), calmodulin antagonists (e.g., H.sub.7) and inhibitors of the sodium/calcium **antiporter** (e.g., **amiloride**); ap-1 inhibitors (for tyrosine kinases, protein kinase C, myosin light chain kinase, Ca.sup.2+ /calmodulin kinase II, casein kinase II); anti-depressants. . .

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L20 ANSWER 10 OF 10 USPATFULL on STN

ACCESSION NUMBER:	1998:14828 USPATFULL
TITLE:	Anti-angiogenic compositions and methods of use
INVENTOR(S):	Hunter, William L., Vancouver, Canada Machan, Lindsay S., Vancouver, Canada Arsenault, A. Larry, Paris, Canada
PATENT ASSIGNEE(S):	Angiogenesis Technologies, Inc., Vancouver, Canada

(non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5716981		19980210
APPLICATION INFO.:	US 1995-478203		19950607 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-417160, filed on 3 Apr 1995, now abandoned which is a continuation-in-part of Ser. No. US 1993-94536, filed on 19 Jul 1993, now abandoned

	NUMBER	DATE
PRIORITY INFORMATION:	WO 1994-CA373	19940719

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Kumar, Shailendra
LEGAL REPRESENTATIVE: Seed and Berry LLP
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 130 Drawing Figure(s); 75 Drawing Page(s)
LINE COUNT: 5084
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . for example: .alpha.-adrenergic blocking agents, angiotensin II receptor antagonists and receptor antagonists for histamine, serotonin, endothelin; inhibitors of the sodium/hydrogen **antiporter** (e.g., **amiloride** and its derivatives); agents that **modulate** intracellular Ca.sup.2+ transport such as L-type (e.g., diltiazem, nifedipine, verapamil) or T-type Ca.sup.2+ channel blockers (e.g., **amiloride**), calmodulin antagonists (e.g., H.sub.7) and inhibitors of the sodium/calcium **antiporter** (e.g., **amiloride**); ap-1 inhibitors (for tyrosine kinases, protein kinase C, myosin light chain kinase, Ca.sup.2+ /calmodulin kinase II, casein kinase II); anti-depressants. . .

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DETD Neovascular **glaucoma** generally occurs as a complication of diseases in which retinal ischemia is predominant. In particular, about one third of the. . . with this disorder have diabetic retinopathy and 28% have central retinal vein occlusion. Other causes include chronic retinal detachment, end-stage **glaucoma**, carotid artery obstructive disease, retrolental fibroplasia, sickle-cell anemia, intraocular tumors, and carotid cavernous fistulas. In its early stages, neovascular **glaucoma** may be diagnosed by high magnification slitlamp biomicroscopy, where it reveals small, dilated, disorganized capillaries (which leak fluorescein) on the. . .

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DETD . . . the vessels and the retina. This results in vitreous hemorrhage

and/or retinal detachment which can lead to blindness. Neovascular angle-closure **glaucoma** is also a complication of this condition.

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=> d his

     (FILE 'HOME' ENTERED AT 18:29:32 ON 27 JUL 2003)

     FILE 'REGISTRY' ENTERED AT 18:29:44 ON 27 JUL 2003
L1             1 S TIMOLOL/CN
L2             1 S AMILORIDE/CN
L3             0 S ETHYL ISOPROPYL AMILORIDE
L4             0 S ISOPROPYL ETHYL AMILORIDE
L5           131 S AMILORIDE
L6             4 S ETHYL AMILORIDE
L7             1 S CARIPORIDE/CN

     FILE 'ADISCTI, ADISINSIGHT, ADISNEWS, BIOSIS, CANCERLIT, CAPLUS, CEN,
     DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL, EMBASE,
     ESBIOBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDICONF, MEDLINE,
     NAPRALERT, NLDB, NUTRACEUT, PASCAL, PCTGEN, ...' ENTERED AT 18:33:21 ON
     27 JUL 2003
L8         31558 S L1 OR TIMOLOL
L9         64288 S L2 OR AMILORIDE
L10          507 S L7 OR ACRIPORIDE
L11         1505 S L7 OR CARIPORIDE
L12        95722 S L8 OR L9 OR L11
L13       159500 S GLAUCOMA
L14        34931 S AQUEOUS HUMOR
L15            0 S S ANTIPORT (S) MODULAT?
L16          457 S ANTIPORT (S) MODULAT?
L17          923 S ANTIPORT? (S) MODULAT?
L18         9965 S L12 AND L13
L19           13 S L18 AND L17
L20           10 DUP REM L19 (3 DUPLICATES REMOVED)

=> s intraocular pressure
  29 FILES SEARCHED...
L21        82563 INTRAOCULAR PRESSURE

=> s l18 and l21
L22         5371 L18 AND L21

=> s l14 and l22
L23          730 L14 AND L22

=> s sodium proton (s) exchange
  33 FILES SEARCHED...
L24         3138 SODIUM PROTON (S) EXCHANGE

=> s l24 and l23
L25            0 L24 AND L23

=> s ae-2 antiport
  21 FILES SEARCHED...
L26            0 AE-2 ANTIPORT

=> s nhe-1 antiport
  26 FILES SEARCHED...
L27            3 NHE-1 ANTIPORT

=> s nhe antiport

L28            3 NHE ANTIPORT

=> s nhe (s) antiport

 75% OF LIMIT FOR L#S REACHED
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L29 206 NHE (S) ANTIPORT

=> s ae2 (s) antiport
L30 30 AE2 (S) ANTIPORT

=> s l29 and l30
L31 4 L29 AND L30

=> s l31 and l23
L32 1 L31 AND L23

=> s l29 or l30

L33 232 L29 OR L30

=> s l23 and l33
L34 1 L23 AND L33

=> d l34 ibib, kwic

L34 ANSWER 1 OF 1 USPATFULL on STN

ACCESSION NUMBER:	2003:120743 USPATFULL
TITLE:	Novel combination therapy to treat **glaucoma**
INVENTOR(S):	Civan, Mortimer M., Wynnewood, PA, UNITED STATES Jacobson, Kenneth A., Silver Spring, MD, UNITED STATES MacKnight, Anthony D.C., Dunedin, NEW ZEALAND Mitchell, Claire H., Philadelphia, PA, UNITED STATES Stone, Richard A., Havertown, PA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003083227	A1	20030501
APPLICATION INFO.:	US 2002-217755	A1	20020813 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2002-9581, filed on 30 Apr 2002, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-133180P	19990507 (60)
	US 2001-312036P	20010813 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Evelyn H. McConathy, Esquire, Dilworth Paxson LLP, 3200 Mellon Bank Center, 1735 Market Street, Philadelphia, PA, 19103
NUMBER OF CLAIMS:	31
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	6 Drawing Page(s)
LINE COUNT:	1250

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Novel combination therapy to treat **glaucoma**

AB Provided is a method for modulating, controlling or regulating **intraocular pressure** and secretion of the **aqueous humor** of the eye, in particular for treating or reducing elevated **intraocular pressure** or secretion, e.g., related to glaucomas. Selected combined drug therapy effectively and synergistically modulates **intraocular pressure** by either (1) double-blocking the uptake step, wherein both transporters in the first (entry step) of **aqueous humor** formation are blocked or inhibited; or (2) blocking the entry and exit steps, wherein the sodium-hydrogen (Na.sup.+/H.sup.+) exchanger underlying the. . . inhibited, and also lowering or reducing the activity of the chloride (Cl.sup.-) channels involved in the second (exit) step of **aqueous humor** formation. By combining the selected drugs or compounds to produce a combined or synergistic modulating effect, control of IOP is. . .

SUMM . . . The present invention relates to the field of ophthalmology. In particular, the invention relates to the prevention and treatment of **glaucoma** and associated elevations of **intraocular**

pressure.

SUMM . . . the world, currently affecting an estimated three million people in the United States, with 300,000 new cases diagnosed every year. **Glaucoma** results from obstructed outflow from the **aqueous humor** of the eye, resulting in elevated **intraocular pressure** in the anterior chamber, and visual loss attributed to progressive damage of the optic nerve, and consequent loss of retinal ganglion cells (Quigley et al., Invest. Ophthalmol. Vis. Sci. 19:505 (1980)). Increase of the **intraocular pressure** ("IOP") of the eye is the major, and best understood, risk factor for the appearance and progression of glaucomatous optic neuropathy. Elevated or increased **intraocular pressure** ("IOP") can also be caused by other conditions, such as impaired intraocular fluid transport caused by eye surgery, including surgery for **glaucoma**. The IOP, itself, reflects a balance between the rates of inflow (fluid formation) and outflow (fluid return) of the **aqueous humor** by re-absorption. Medical approaches to treating **glaucoma** are frequently directed at reducing the rate of net formation of **aqueous humor**.

SUMM [0005] The **aqueous humor** of the eye is formed by the ciliary epithelium, comprising two cell layers, whose apical membranes are juxtaposed. The outer. . . ciliary epithelial (PE) cells face the stroma, while the inner non-pigmented ciliary epithelial (NPE) cells are in contact with the **aqueous humor**. Secretion involves primary solute transfer, primarily NaCl, with accompanying water movement, from the blood or supporting stroma, across the basolateral membranes of the PE cells into the **aqueous humor** in the contralateral posterior chamber of the eye (Cole, Exp. Eye Res. 25(Suppl):161-176 (1977)). This provides an osmotic driving force. . .

SUMM [0006] The secretion of **aqueous humor** into the eye results as a consequence of two opposing physiological processes: fluid secretion into the eye by the NPE. . . of the eye) by the PE cells. Thus, both release of chloride ions by the NPE cells into the adjacent **aqueous humor** enhance secretion, and chloride ion release by the PE cells into the neighboring stroma reduce net secretion (Civan, Current Topics. . . Membranes 45:1-24 (1998), Tripathi, In: The Eye, Chap. 3, pp 163-356, Davson & Graham (eds), Academic Press, New York, (1974)). **Intraocular pressure** reflects a balance between the rates of secretion and outflow of the **aqueous humor**.

SUMM . . . factor governing the rate of secretion is the rate of chloride ion (Cl.sup.-) release from the NPE cells into the **aqueous humor** (Civan, News Physiol. Sci. 12:158-162 (1997)). Thus, the activity of the Cl.sup.- channels is a rate-limiting factor in **aqueous humor** secretion, given the low baseline level of channel activity and the predominance of the chloride anion in the transferred fluid. . .

SUMM [0008] Structurally the mouse eye parallels the **aqueous humor** outflow pathways in the human and shows similar functional responses to drugs that inhibit **aqueous humor** inflow and facilitate outflow in the human. Thus, the mouse is a particularly suitable non-primate model for studying the genetic. . . control of physiological and pharmacological function. However, the anterior chamber of a mouse eye contains only about 2-4 .mu.l of **aqueous humor**, which until recently, complicated efforts to measure IOP in the mouse reliably.

SUMM [0010] FIG. 1 depicts a minimalist, and necessarily incomplete, consensus model of **aqueous humor** secretion from Avila et al., Invest. Ophthalmol. Vis. Sci. 43:1897-1902 (2002) (Carre et al., Curr. Eye Res. 11:609-624 (1992); Chu. . . et al., Exp. Eye. Res. 64:945-952 (1997)). "Inflow," the transfer of fluid from body side or "stromal side" into the **aqueous humor**, is presented as basically a 3-step process. First, as shown, water and salt, NaCl, is initially taken up from the. . .

SUMM . . . the PE cells diffuses across the gap junctions into the second cell layer [non-pigmented ciliary epithelial (NPE) cells] abutting the **aqueous humor** (Coca-Prados et al., Curr. Eye Res. 11:113-122 (1992); Edelman et al., 1994; Mitchell et al., FASEB J

11:A301 (1998); Oh. . . (1994); Raviola et al., Invest. Ophthalmol. Vis. Sci. 17:958-981 (1978); Walker et al., 1999; Wolosin et al., In: The Eye's **Aqueous Humor**: From Secretion to **Glaucoma**, Civan (ed), Academic Press, Boston, pp 135-162 (1998)).

SUMM [0012] Finally, the salts and fluids are released into the **aqueous humor** by the contiguous NPE cells through the Na.sup.+, K.sup.+-activated ATPase exchange pump and Cl.sup.- channels (Jacob et al., Am. J.. . .

SUMM [0014] Current treatment methods to relieve **intraocular pressure** include forming small laser penetrations in the eye to release excess pressure (e.g., trabeculectomy), as well as the use of systemic and topical drugs for lowering **intraocular pressure**. At the present time, medical control of **intraocular pressure** and **glaucoma** consists of topical, oral or intravitreous administration of many compounds. See generally, Horlington, U.S. Pat. No. 4,425,346; Komuro et al.,. . .

SUMM [0015] Among the most effective medical therapies for **glaucoma** are strategies aimed at reducing **intraocular pressure** by reducing the net rate of **aqueous humor** formation by the ocular ciliary epithelial bilayer (see generally, Shields, Textbook of **Glaucoma**, 3rd Ed., Williams & Wilkins, Baltimore (1992)). This can occur either by blocking unidirectional secretion from stroma to the **aqueous humor** or by stimulating flow in the opposite direction (Caprioli et al., Yale J. Biol. Med. 57:283-300 (1984); Civan et al.,. . .

SUMM [0016] Four primary classes of drugs are used to treat **glaucoma**. These include: miotics (e.g., pilocarpine, carbachol and acetylcholinesterase inhibitors); sympathomimetics (e.g., epinephrine, metipranolol, dipivefrin, carbachol, dipivalyl, and parn-aminoclonidine); beta-blockers (e.g., betaxolol, levobunolol and **timolol**) and potent cholinesterase inhibitors (e.g., echothiophate); and carbonic anhydrase inhibitors (e.g., acetazolamide, methazolamide, dorzolamidet and ethoxzolamide). For example, miotics and sympathomimetics are believed to lower **intraocular pressure** by increasing the outflow of **aqueous humor**, while beta-blockers and carbonic anhydrase inhibitors are believed to operate by decreasing the formation of **aqueous humor** (Ritch et al., (1996) In: The Glaucomas (eds Ritch, Shields, Krupin) 2nd ed., pp. 1507-1519, Mosby, St. Louis). The non-selective,. . . topical, .beta.- and .beta..sub.1-adrenergic antagonists have proven to be useful for lowering the secretory rate of fluids in the eye (**aqueous humor** inflow), and thereby for controlling **intraocular pressure** (Gieser et al., (1996) In: The Glaucomas, supra, pp. 1425-1448). **Timolol** reportedly binds to .beta.-adrenergic receptors of the ciliary processes with high affinity (Vareilles et al., Invest. Ophthalmol. Vis. Sci. 16:987-996 (1977)), and is among the most widely used and effective drugs for lowering the **intraocular pressure** of glaucomatous patients (Gieser et al., 1996). Another new type of drug, precursor prostaglandin compounds (e.g., latanoprost), which enhance outflow. . .

SUMM . . . Miotics tend to reduce the patient's visual acuity, particularly in the presence of lenticular opacities. Topical beta blockers, such as **timolol**, have been associated with side-effects such as fatigue, confusion, or asthma; while exacerbated cardiac symptoms have been reported after rapid. . .

SUMM [0018] Accordingly, because of the insidious nature of glaucomas and other conditions affecting the **intraocular pressure** in the eye and the difficulties in treating them, there has been an on-going and long-felt need in the art for the development of methods for the safe and reliable prevention, control or treatment of elevated **intraocular pressure**, that can be utilized before significant damage to the optical nerve occurs. Also needed is the discovery of compositions or. . .

SUMM [0019] Lower than normal **intraocular pressure** can also be problematic, caused for example, by a variety of conditions, such as surgery for **glaucoma**, retinal detachment, uveitis, and the like. However, since no drugs are presently available for the safe

and effective prevention, modulation or regulation of reduced **intraocular pressure** without adverse side-effects, there remains a need for the development of more effective treatment methods for surgically-induced low or depressed **intraocular pressure**, as well as elevated **intraocular pressure**.

SUMM [0020] The present invention, therefore, meets a particular need in the art by providing methods for preventing, modulating or regulating **intraocular pressure**, in particular for treating or reducing elevated **intraocular pressure**. Specifically, the present invention provides combined therapeutic methods by which intraocular fluid pressure can be selectively and reversably increased, decreased,. . . level, although primarily the invention will be useful to relieve or prevent elevated levels of intraocular fluid in, for example, **glaucoma** patients, before vision is adversely and permanently affected. In addition, the present combined therapeutic methods permit known compounds to be. . .

SUMM [0021] The present invention provides several methods for regulating, controlling or modulating **aqueous humor** secretion, comprising the step of administering to ciliary epithelial cells of the **aqueous humor**, an effective ("secretion-modulating") amount of more than one pharmaceutical compositions administered in combination (or sequentially, but in sufficiently close proximity. . . combined effect). Further provided is in vivo evidence that the combinations of drugs or therapeutic moieties effectively and synergistically lower **intraocular pressure** (IOP) by: (1) double-blocking the uptake step, wherein both transporters in the first (entry step) of **aqueous humor** formation (the paired Na.sup.+/H.sup.+ and Cl.sup.-/HCO.sub.3.sup.- antiports and the Na.sup.+-K.sup.+-2Cl.sup.- symport) are blocked or inhibited; or (2) blocking or inhibiting. . . and also the activity is lowered or reduced of the chloride (Cl.sup.-) channels involved in the second (exit) step of **aqueous humor** formation.

SUMM . . . in the patient, thereby modulating, preferably by blocking or inhibiting elevated IOP. In fact, when either the secretion into the **aqueous humor** cells is elevated, or the fluid pressure or **intraocular pressure** is elevated in a patient, the drugs in the combination therapy are administered in a combined amount, that is sufficient. . .

SUMM . . . to the cells in vitro or in vivo. The latter methods offer regulation, control or modulation of fluid pressure or **intraocular pressure** in an individual or subject.

DRWD [0026] FIG. 1 depicts a consensus model of **aqueous humor** formation and NaCl secretion by the ciliary epithelium. Carbonic anhydrase limited delivery of H.sup.+ and HCO.sub.3.sup.- limits uptake of stromal. . . through the Na.sup.+-K.sup.+-2Cl.sup.- symport. At the contralateral surface, Na+ and Cl.sup.- can be released from the NPE cells into the **aqueous humor** through Na.sup.+, K.sup.+-activated ATPase and Cl.sup.- channels, respectively.

DETD [0031] The methods and compositions of the present invention are intended for treatment of **glaucoma** and other conditions, which manifest elevated **intraocular pressure** in the eye of a patient, particularly human patients, but also including other mammalian hosts. **Glaucoma** is a term which embraces a group of ocular diseases characterized by elevated **intraocular pressure** levels which can damage the eye, and destroy the optic nerve and related ganglia. In addition, normotensive **glaucoma** is characterized by an apparent nonelevated **intraocular pressure**. However, for the patient suffering from normotensive **glaucoma**, the apparently normal pressure is sufficiently high for that particular patient as to cause the same types of nerve and. .

DETD [0032] Therefore, the glaucomas treated by the methods of the present invention are not limited exclusively to elevated **intraocular pressure**. Other conditions which result in elevated **intraocular pressure** levels include cataract surgery, steroid treatment, and treatment with other drugs known to cause **intraocular pressure**. The methods and compositions of the present invention are intended to treat all such conditions,

preferably to lower the **intraocular pressure** to a manageable and safe level. Moreover, the methods are also effective in the treatment of lower than normal **intraocular pressure** levels.

DETD . . . present invention provides in vivo evidence that combinations of drugs or therapeutic moieties (the "combined modulator") effectively and synergistically lower **intraocular pressure** (IOP) by either: (1) double-blocking of uptake step, wherein both transporters in the first (entry step) of **aqueous humor** formation are blocked or inhibited; or (2) blocking of the entry and exit steps, wherein the sodium-hydrogen (Na.sup.+/H.sup.+) exchanger underlying. . . and also the activity is lowered or reduced of the chloride (Cl.sup.-) channels involved in the second (exit) step of **aqueous humor** formation. These discoveries, which are discussed in detail below, permit strategies to be developed to use drugs at very low, focussed concentrations for preventing, modulating or regulating **intraocular pressure**, most particularly for treating or reducing elevated **intraocular pressure** .

DETD [0038] The basis for the first step in inflow into the **aqueous humor**, uptake of salt into the PE-cell layer, has been the subject of considerable controversy. Some investigators have reported that the. . .

DETD . . . in vitro (in cultured bovine PE cells and RNA preparations of human ciliary body) the molecular basis for the paired **antiport** activity of the **NHE**-1 Na.sup.+/H.sup.+ exchanger, and the **AE2** Cl.sup.-/HCO.sub.3.sup.- exchanger. (Counillon et al., Pflugers Arch. (Eur. J. Physiol.) 440:667-678 (2000); Avila et al., 2001A). Because the **NHE**-1 exchanger is highly sensitive to several blockers of the sodium/proton symport, it was possible to selectively block the exchangers specifically involved in **aqueous humor** inflow.

DETD . . . antiports provide the dominant entry pathway under physiological conditions, and further suggested that carbonic anhydrase inhibitors (commonly used to treat **glaucoma**) act by blocking Na.sup.+/H.sup.+ exchange. More recently an electron-probe X-ray microanalysis (McLaughlin et al., Am. J. Physiol. Cell Physiol. 281:C865-C875(2001)) further suggested that another very widely used antiglaucomatous drug (**timolol**) acts primarily in the same way, blocking Na.sup.+/H.sup.+ exchange.

DETD . . . Ophthamol. Vis. Sci. 38:1700-1707 (1997). However, in a preferred and exemplified embodiment of the invention, after applying a topical inhibitor (ethylisopropyl-**amiloride**) of Na.sup.+/H.sup.+ antiport exchange, the administration of 10 mM bumetanide reduced IOP by 4.0.+-.0.6 mm Hg (mean.+-.SE, N=6, P<0.01). By. . .

DETD [0043] The basis of the release step of solute and water into **aqueous humor** is generally via extrusion of Na.sup.+ through the Na.sup.+, K.sup.+-activated ATPase and the release of Cl.sup.- through the Cl.sup.- channels. Agonists of A.sub.3-subtype adenosine receptors have been found to activate the Cl.sup.- channels of NPE cells. This action enhances **aqueous humor** inflow and raises IOP.

DETD . . . the present invention provides an alternative combinatorial drug approach for more effectively controlling IOP, wherein both the first step of **aqueous humor** formation (entry into the ciliary epithelium) and the release step of the chloride ions from the **aqueous humor** are simultaneously blocked. The advantage of this approach is that each of the two steps can be selectively targeted, thereby. . . two entry steps were blocked, the NHE-1 exchanger can be selectively blocked, which is important in the first step of **aqueous humor** formation. However, it is also possible to block activation of the final step of **aqueous humor** formation by applying A.sub.3-subtype adenosine-receptor antagonists. Therefore, by administering both classes of drugs together, the effect is highly advantageous (blocking or controlling both the first and the final steps of **aqueous humor** formation), resulting in an efficacious mechanism for modulating IOP that is also relatively free of side effects.

DETD . . . and it is desirable that such elevated pressures be lowered to below 18 mm Hg. In the case of low-tension **glaucoma**, it is desirable for the **intraocular pressure** to be lowered below that exhibited by the patient prior to treatment. **Intraocular pressure** can be measured by conventional tonometric techniques.

DETD [0047] The methods and compositions of the present invention are also intended for treatment of hypotonia and/or reduced **intraocular pressure** conditions of the eye. Reduced intraocular pressures are generally considered below about 8 mm Hg. Such conditions may result from a variety of causes, such as surgery for **glaucoma**, retinal detachment, uveitis, and the like.

DETD [0048] The exemplified inhibitors described in detail in the Examples include **cariporide**, EIPA (ethylisopropylamiloride), DMA (dimethylamiloride) and **amiloride**, at concentrations characteristic of the NHE-1 isoform. Nevertheless, applicable compounds would include any of the beta blockers (including topical, .beta.- and .beta..sub.1-adrenergic antagonists, such as **timolol**), or **amiloride** analogs, as well as, but not limited to, the many compounds produced by Hoechst, i.e., **cariporide**, as well as other compounds that would be recognized as modulators of Na.sup.+ uptake or the anion exchange system. See,. . .

DETD [0049] In the present invention, a pharmaceutical composition which upon administration increases or decreases secretion of fluids into the **aqueous humor** as compared to the level prior to administration, is termed a "secretion modulator;" and the amount of the modulator necessary. . . is termed the "secretion modulating amount." Similarly, a pharmaceutical composition which upon administration increases or decreases fluid pressure in the **aqueous humor** or **intraocular pressure**, as compared to the level prior to administration, is termed a "pressure modulator;" and the amount of the modulator necessary. . .

DETD . . . composition, which can include drugs, compounds, pharmaceuticals or the like, can be used to treat an individual, such as a **glaucoma** patient.

DETD [0052] Potential physiologic implications. The **NHE**-1 isoform of the Na.sup.+/H.sup.+ exchangers is ubiquitously expressed in all eukaryotic cells (Counillon et al., J. Biol Chem 275:1-4 (2000). . . . solute and fluid by the PE cells (the post-RVD RVI). This fluid uptake can be inhibited by blocking the Na.sup.+/H.sup.+ **antiport** with dimethylamiloride or by blocking Cl.sup.-/HCO.sub.3.sup.- exchange by omitting CO.sub.2/HCO.sub.3.sup.-. When the Na.sup.+-K.sup.+-2Cl.sup.- symport is blocked with bumetanide, the further addition of DIDS also blocks the post-RVD RVI. Thus, the paired exchange of **NHE**-1 and **AE2** can lead to net fluid uptake from the extracellular compartment into the PE cells, as demonstrated in other systems (Jiang. . .

DETD . . . and Cl.sup.-/HCO.sub.3.sup.- antiports) and the effect of blocking both, also explains the clinical efficacy of carbonic anhydrase inhibitors in treating **glaucoma**. Reducing the availability of H.sup.+ and HCO.sub.3.sup.- to both antiports, thereby synergistically inhibits the initial step in **aqueous humor** secretion. The current data suggest that this step could be selectively blocked in glaucomatous patients by specifically inhibiting NHE-1 with low concentrations of EIPA, DMA or **cariporide**, particularly in combination with bumetanide to simultaneously block the symport.

DETD . . . A therapeutically effective amount of the combined agent is that amount necessary to significantly reduce or eliminate symptoms associated with **glaucoma**, particularly to reduce or prevent elevated IOP more effectively that the effect of one of the compositions alone would have.. . .

DETD The Control of Sodium/Proton Exchangers to Control the Secretion of Excess Fluids into the **Aqueous Humor**

DETD . . . However, first it was necessary to confirm that the paired antiports are the dominant mechanism in the first step of **aqueous humor** formation. Consequently, one or the other antiport was blocked to measure whether inflow, and therefore IOP, are reduced by the. . .

DETD [0076] After entry of the tip into the anterior chamber, the step change

in hydrostatic pressure forced **aqueous humor** into the micropipette, displacing the low-resistance 3-M KCl filling solution from the tip back toward the shank. The resultant increase. . . electrical resistance generated a signal to a vacuum-pressure pump that produced an equal counter-pressure that maintained the position of the **aqueous humor**-KCl interface at the tip of the micropipette, and thus sustains the original electrical resistance. This counter-pressure equaled the hydrostatic pressure. . .

DETD . . . Fishers, N.Y.) and a piezoelectric step driver (model PZ100; Burleigh). IOP was monitored after positioning the micropipette tip in the **aqueous humor**. The baseline IOP in the present study was 14.2.+-.0.4 mm Hg (n=113). In measuring drug-induced changes in IOP, each animal. . .

DETD [0084] Among the drugs administered were the selective Na.sup.+/H.sup.+ **antiport** inhibitors (direct inhibitors), dimethylamiloride (DMA) and ethylisopropylamiloride (EIPA) (Sigma Chemical Co). A third such inhibitor also used was BIIB723 (Boehringer/Ingelheim, Biberach an der Riss, Germany), which is a member of the BIIB family of Na.sup.+/H.sup.+ **antiport** blockers. Similar to nearly all other **NHE**-1 inhibitors, BIIB723 is an acylguanidine, displaying a selectivity for **NHE**-1 over **NHE**-2 of approximately 40-fold and an IC.sub.50 of approximately 30 nM in cardiomyocytes and approximately 100 nM in hamster fibroblasts. The parent compound (**amiloride**; Merck, Rahway, N.J.) of the **amiloride** analogues DMA and EIPA is a low-potency inhibitor of both Na.sup.+/H.sup.+ and Na.sup.+/Ca.sup.2+ antiports and a higher-potency blocker of ENaC. . .

DETD [0087] DMA, an **amiloride** analogue with a highly selective inhibitory effect on the **NHE**-1 **antiport** (Counillon et al., Mol. Pharmacol. 44:1041-1045 (1993)) produced a concentration-dependent lowering of IOP (FIG. 3, Table 1). Although the precise. . .

DETD [0088] Another **amiloride** analogue, EIPA, displayed the same minimally effective droplet concentration and enhanced lowering of IOP at 3 mM (300 ng; by 4.1.+-.1.0 mm Hg, Table 1). A third acylguanidine **antiport** inhibitor, BIIB723, produced a maximal hypotensive effect at 3 mM (16.0 .mu.g) of 4.9.+-.1.7 mm Hg, similar to that of. . . .mu.g; -4.5.+-.0.5 mm Hg) and 3 mM (16.0 .mu.g; -4.9.+-.1.7 mm Hg) and the similar reductions produced by all three **NHE**-1 inhibitors tested at 3 mM indicated that a maximal IOP reduction was achieved of 4.1 to 5.0 mm Hg. The. . . IOP.

TABLE 1

Single-Drug Effects of DMA, EIPA, Bumetanide, BIIB723, and Dorzolamide on IOP.

Drug	Class	n	Conc.	Dose	.DELTA.IOP(mm Hg)	P
DMA	Na/H **antiport** inhibitor	3	100 .mu.M	294 ng	+0.9 .+-. 0.9	
		23	1 mM	2.94 .mu.g	-3.8 .+-. 0.5	<0.001
		4	3 mM	8.82 .mu.g	-5.0 .+-. 0.7	<0.01
EIPA	Na/H **antiport** inhibitor	3	100 .mu.M	300 ng	+0.8 .+-. 0.2	
		10	1 mM	3.00 .mu.g	-2.6 .+-. 0.5	<0.001
		6	3 mM	9.00 .mu.g	-4.1 .+-. 1.0	<0.01
BIIB	Na/H **antiport** inhibitor	3	10 .mu.M	53.4 ng	-0.4 .+-. 1.9	
		4	100 .mu.M	534 ng	-2.7 .+-. 0.4	<0.01
		17	1. . .			

DETD . . . of 1 mM for DMA and EIPA (Table 1) appears to correspond to approximately 1 to 10 .mu.M in the **aqueous humor**, and the minimally effective droplet concentration of 100 .mu.M for BIIB723 corresponded to **aqueous humor** concentrations

of .about.0.1 to 1 .mu.M. The differences may arise from a higher penetrance for BIIB723, because the IC.sub.50 observed. . .

DETD . . . that topical application of dorzolamide also reduces IOP, albeit to a lesser extent at the droplet concentrations applied (Table 1). **Amiloride**, which inhibits NHE-1 antiports at a potency 1 to 2 orders of magnitude lower than the **amiloride** analogues DMA and EIPA (Counillon et al., 2000), itself exerted no significant effect on mouse IOP at a droplet concentration. . . of 1 mM (2.30 .mu.g, n=7, data not shown). To reach a 10-mM concentration, it was necessary to solubilize the **amiloride** in 30% DMSO. After pretreatment with vehicle containing 30% DMSO, subsequent application of 10 mM **amiloride** in the same concentration of vehicle did not alter that IOP (.DELTA.IOP=1.0.+-.0.7 mm Hg, n=4, P>0.2). Thus, at a concentration 10 times higher than EIPA's minimal effective concentration, **amiloride** had no effect, consistent with the known ratio of the potency of these inhibitors (3.9:0.07 .mu.M, or .about.56) when applied. . .

DETD [0091] In contrast to the IOP reductions triggered by the three selective inhibitors of the **NHE**-1 **antiport** at droplet concentrations of 0.1 to 3 mM (Table 1), blockage of the Na.sup.+-K.sup.+-2Cl.sup.- symport with droplet concentrations of 0.1. . .

DETD [0095] In sum, these salient findings demonstrate that inhibitors of the **NHE**-1 Na.sup.+/H.sup.+ **antiport** reduced IOP at 1-mM droplet concentrations, but the far less potent parent compound (**amiloride**) had no effect on IOP at tenfold higher concentration. Topical application of the carbonic anhydrase inhibitor dorzolamide reduced IOP in. . . mouse. Similarly, application of a selective Na.sup.+-K.sup.+-2Cl.sup.- symport inhibitor (bumetanide) itself had no significant effect. However, after first inhibiting the **NHE** antiports, either directly with acylguanidine blockers or indirectly with dorzolamide, the subsequent application of bumetanide triggered a highly significant further. . .

DETD Determining the Combined Effect in Vivo of Selective Blocking of Entry and Release Steps in **Aqueous Humor** Formation

DETD . . . by selectively and simultaneously (or by producing a combined effect in the patient) blocking both (1) the first step of **aqueous humor** formation (entry into the ciliary epithelium), and (2) the release step of Cl.sup.- from the **aqueous humor**. As discussed with regard to the entry step above, the NHE-1 exchanger can be selectively blocked or inhibited, which is important in the first step of **aqueous humor** formation. However, it is also possible to block activation of the final step of **aqueous humor** formation by applying, e.g., A.sub.3-subtype adenosine-receptor antagonists.

DETD . . . and analysis procedures as described in Example 2, to demonstrate the effect of blocking both entry and exit steps of **aqueous humor** formation in a test animal, an A.sub.3AR-knockout mice. The observations that A.sub.3AR agonists activate Cl.sup.- channel led to the hypothesis that these agonists would increase **aqueous humor** secretion and thereby IOP in vivo, and that A.sub.3AR antagonists would exert the opposite effects. In the absence of the. . .

DETD . . . the exit step (FIG. 5), blocking the entry step (with acetazolamide), reduced IOP even further by 2-3 mm Hg. The **intraocular pressure** cannot fall below the episcleral venous pressure, which in humans has been estimated to be 8.0-11.5 mm Hg. Thus, the. . .

DETD . . . effectively and synergistically lower IOP by: (1) double-blocking of uptake step, wherein both transporters in the first (entry step) of **aqueous humor** formation are blocked or inhibited; or (2) blocking of the entry and exit steps, wherein the sodium-hydrogen (Na/H) exchanger underlying. . . and also the activity is lowered or reduced of the chloride (Cl.sup.-) channels involved in the second (exit) step of **aqueous humor** formation.

CLM What is claimed is:

1. A method for regulating, controlling or modulating **aqueous humor** secretion, comprising the step of administering to ciliary

epithelial cells of the **aqueous humor**, an effective secretion-modulating amount of a combined modulator, which is, or forms, a combination of pharmaceutical compositions comprising an effective. .

4. The method of claim 1, wherein both transporters in the entry step of **aqueous humor** formation (the paired Na.sup.+/H.sup.+ and Cl.sup.-/HCO.sub.3.sup.- antiports and the Na.sup.+-K.sup.+-2Cl.sup.- symport) are blocked.

5. The method of claim 1, wherein secretion in the **aqueous humor** cells is elevated, and wherein the combined modulator is administered in an amount sufficient to reduce the elevated secretion.

6. The method of claim 1, wherein the method of regulating, controlling or modulating **aqueous humor** secretion further comprises regulating, controlling or modulating fluid pressure in the **aqueous humor** ciliary epithelial cells.

8. The method of claim 1, wherein the Na.sup.+/H.sup.+ exchange occurs at the **NHE**-1 **antiport**.

9. The method of claim 1, wherein the Cl.sup.-/HCO.sub.3.sup.- exchange occurs at the **AE2 antiport**.

13. The method of claim 12, wherein the modulating effect occurs in the formation of the **aqueous humor** of a human patient, comprising the step of administering to the patient an effective **intraocular pressure**-modulating amount of the combined modulator.

16. The method of claim 1, wherein the regulating, controlling or modulating effect of administering the combined modulator on **aqueous humor** formation is synergistic, as compared with an additive combination of the independent pharmaceutical compositions forming the combined modulator.

18. A method for regulating, controlling or modulating **aqueous humor** secretion, comprising the step of administering to ciliary epithelial cells of the **aqueous humor**, an effective secretion-modulating amount of a combined modulator which is, or forms, a combination of pharmaceutical compositions comprising at least one modulator that blocks or inhibits at least one entry step in the formation of the **aqueous humor** and at least one modulator that activity is lowers or reduces the activity of at least one exit step in the formation of the **aqueous humor**.

20. The method of claim 18, wherein chloride (Cl.sup.-) channels activity, involved in the exit step of **aqueous humor** formation, is lowered or reduced.

21. The method of claim 18, wherein secretion in the **aqueous humor** cells is elevated, and wherein the combined modulator is administered in an amount sufficient to reduce the elevated secretion.

22. The method of claim 18, wherein the method of regulating, controlling or modulating **aqueous humor** secretion, further comprises regulating, controlling or modulating fluid pressure in the **aqueous humor** ciliary epithelial cells.

27. The method of claim 26, wherein the modulating effect occurs in the formation of the **aqueous humor** of a human patient, comprising the step of administering to the patient an effective **intraocular pressure**-modulating amount of the combined modulator.

30. The method of claim 18, wherein the regulating, controlling or modulating effect of administering the combined modulator on **aqueous humor** formation is synergistic, as compared with an additive combination of the independent pharmaceutical

compositions forming the combined modulator.

IT **2609-46-3**, Amiloride
(combination therapy to treat glaucoma by controlling secretion of excess fluids into aq. humor)

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L1 1 S TIMOLOL/CN
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L4 0 S ISOPROPYL ETHYL AMILORIDE
L5 131 S AMILORIDE
L6 4 S ETHYL AMILORIDE
L7 1 S CARIPORIDE/CN

FILE 'ADISCTI, ADISINSIGHT, ADISNEWS, BIOSIS, CANCERLIT, CAPLUS, CEN, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL, EMBASE, ESBIOBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDICONF, MEDLINE, NAPRALERT, NLDB, NUTRACEUT, PASCAL, PCTGEN, ...' ENTERED AT 18:33:21 ON 27 JUL 2003
L8 31558 S L1 OR TIMOLOL
L9 64288 S L2 OR AMILORIDE
L10 507 S L7 OR ACRIPORIDE
L11 1505 S L7 OR CARIPORIDE
L12 95722 S L8 OR L9 OR L11
L13 159500 S GLAUCOMA
L14 34931 S AQUEOUS HUMOR
L15 0 S S ANTIPORT (S) MODULAT?
L16 457 S ANTIPORT (S) MODULAT?
L17 923 S ANTIPORT? (S) MODULAT?
L18 9965 S L12 AND L13
L19 13 S L18 AND L17
L20 10 DUP REM L19 (3 DUPLICATES REMOVED)
L21 82563 S INTRAOCULAR PRESSURE
L22 5371 S L18 AND L21
L23 730 S L14 AND L22
L24 3138 S SODIUM PROTON (S) EXCHANGE
L25 0 S L24 AND L23
L26 0 S AE-2 ANTIPORT
L27 3 S NHE-1 ANTIPORT
L28 3 S NHE ANTIPORT
L29 206 S NHE (S) ANTIPORT
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DOCUMENT NUMBER: 132:44914
TITLE: Puerarin eyedrops: reduction of **intraocular pressure** and determination in **aqueous humor**

AUTHOR(S): Yan, Han-Ying; Zhu, Yan-Qin; Wu, Zheng-Hong; Chen, Guang-Xin
CORPORATE SOURCE: Research Center of Ocular Pharmacology, Jiangsu Provincial Institute of Materia Media, Nanjing, 210009, Peop. Rep. China
SOURCE: Yanke Xinjinzhan (1999), 19(2), 73-77
CODEN: YAXIF2; ISSN: 1003-5141
PUBLISHER: Yanke Xinjinzhan Zazhi Bianweihui
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

TI Puerarin eyedrops: reduction of **intraocular pressure** and determination in **aqueous humor**

AB Chronic ocular hypertension was produced in rabbits by injection of dexamethasone (0.5 mg every other day for 3 wk) into the bulbar subconjunctiva of the superior corneal margin of the rabbit eye; acute ocular hypertension was induced by rapid i.v. injection of glucose at 15 mg/kg. A reversed-phase HPLC method with UV detection was used to det. puerarin in aq. humor. The potency of 10 g puerarin/L in reducing intraocular hypertension was similar to that of 5 g **timolol**/L, but the duration of action of puerarin was longer than that of **timolol**. The pharmacokinetic parameters of puerarin in the aq. humor were: t1/2.alpha. = 0.69 h; t1/2.beta. = 8.32 h; Cmax = 0.963 mg/L; AUC = 5.16 mg/h/L; tmax = 2.0 h. Thus, 10-g/L puerarin eyedrops can decrease intraocular hypertension induced by i.v. injection of glucose and topical dexamethasone. The reversed-phase HPLC-UV method used is simple and sensitive for the detn. of puerarin in aq. humor.

ST puerarin eyedrop intraocular hypertension aq humor HPLC; **glaucoma** puerarin eyedrop

IT Eye
(aq. humor; puerarin eyedrops: redn. of **intraocular pressure** and detn. in aq. humor by HPLC)

IT **Glaucoma** (disease)
(puerarin eyedrops: redn. of **intraocular pressure** and detn. in aq. humor by HPLC)

IT Drug delivery systems
(solns., ophthalmic; puerarin eyedrops: redn. of **intraocular pressure** and detn. in aq. humor by HPLC)

IT 3681-99-0, Puerarin
RL: ANT (Analyte); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)
(puerarin eyedrops: redn. of **intraocular pressure** and detn. in aq. humor by HPLC)

L35 ANSWER 171 OF 552 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 1999:737621 SCISEARCH
THE GENUINE ARTICLE: 238ZB
TITLE: Metabolites of isopropyl unoprostane as potential ophthalmic solutions to reduce **intraocular pressure** in pigmented rabbits
AUTHOR: Kashiwagi K (Reprint); Iizuka Y; Tsukahara S
CORPORATE SOURCE: YAMANASHI MED UNIV, DEPT OPHTHALMOL, YAMANASHI 4093898, JAPAN (Reprint)
COUNTRY OF AUTHOR: JAPAN
SOURCE: JAPANESE JOURNAL OF PHARMACOLOGY, (SEP 1999) Vol. 81, No. 1, pp. 56-62.
Publisher: JAPANESE PHARMACOLOGICAL SOC, EDITORIAL OFF, KANTOHYA BLDG GOKOMACHI-EBISUGAWA NAKAGYO-KU, KYOTO 604, JAPAN.
ISSN: 0021-5198.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 21

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

TI Metabolites of isopropyl unoprostane as potential ophthalmic solutions to reduce **intraocular pressure** in pigmented rabbits

AB . . . rabbits to clarify which metabolites are involved in actions in the eye. Tritium-labeled isopropyl unoprostone eyedrops were

administered. The cornea, **aqueous humor**, iris, ciliary body and retina were then collected at 5, 15 or 30 min or at 2, 6 or 12. . . M1, and the further metabolized compound, M2, were detected; and the concentrations of these metabolites decreased with time. In the **aqueous humor**, M1, M2 and another metabolite, M3, were detected, with peak concentrations of M1 at 30 min and M2 at 2. . . iris and ciliary body showed a similar metabolism with peak concentrations of M1 and M2 at 30 min. In the **aqueous humor**, iris and ciliary body, M2 was the dominant metabolite from 30 min. In the retina, only total radioactivity was detected.. . .

ST Author Keywords: isopropyl unoprostone; prostaglandin; **glaucoma**; metabolism; esterase

STP KeyWords Plus (R): PROSTAGLANDIN-RELATED COMPOUND; **AQUEOUS-HUMOR** DYNAMICS; TOPICAL APPLICATION; UF-021; **GLAUCOMA**; EYES; PHARMACOKINETICS; **TIMOLOL**; DRUG; IRIS

L35 ANSWER 172 OF 552 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN

ACCESSION NUMBER: 2000060014 EMBASE

TITLE: Brimonidine 0.2% behaviour on **intraocular pressure** in **Timolol**-uncontrolled glaucomatous patients.

AUTHOR: Centofanti M.; Manni G.L.; Gregori D.; Parisi V.; Cocco F.; Bucci M.G.

CORPORATE SOURCE: M. Centofanti, Eye Clinic, University 'Tor Vergata' of Rome, Roma, Italy

SOURCE: Acta Ophthalmologica Scandinavica, Supplement, (1999) 77/229 (52).
Refs: 5
ISSN: 1395-3931 CODEN: AOSSFB

COUNTRY: Denmark

DOCUMENT TYPE: Journal; Conference Article

FILE SEGMENT: 012 Ophthalmology
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

TI Brimonidine 0.2% behaviour on **intraocular pressure** in **Timolol**-uncontrolled glaucomatous patients.

CT Medical Descriptors:
***glaucoma: DT, drug therapy**
***intraocular pressure**
aqueous humor flow
drug binding
drug efficacy
open angle glaucoma: DT, drug therapy
pressure volume curve
pulsatile drug release
receptor affinity
tonometry
human
clinical article
male
female
aged
adult
conference paper
priority journal
*alpha adrenergic receptor stimulating agent: CM, drug. . .
pharmacology
*alpha adrenergic receptor stimulating agent: TP, topical drug administration
*brimonidine: CM, drug comparison
*brimonidine: DT, drug therapy
*brimonidine: PD, pharmacology
*brimonidine: TP, topical drug administration
***timolol: DT, drug therapy**
alpha 2 adrenergic receptor: EC, endogenous compound
apraclonidine: CM, drug comparison
beta adrenergic receptor blocking agent: DT, drug therapy
clonidine: CM,. . .

RN (brimonidine) 59803-98-4; (**timolol**) **26839-75-8**;
(apraclonidine) 66711-21-5; (clonidine) 4205-90-7, 4205-91-8, 57066-25-8

L35 ANSWER 173 OF 552 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 2000:160250 SCISEARCH
THE GENUINE ARTICLE: 286HX
TITLE: Brimonidine 0.2(behaviour on **intraocular pressure** in **Timolol**-uncontrolled glaucomatous patients
AUTHOR: Centofanti M (Reprint); Manni G L; Gregori D; Parisi V; Cocco F; Bucci M G
CORPORATE SOURCE: UNIV ROMA TOR VERGATA, EYE CLIN, ROME, ITALY (Reprint); GB BIETTI FDN OPHTHALMOL, ROME, ITALY; FATEBENEFRATELLI HOSP, OCULUST DIV, AFAR CRCCS, ROME, ITALY
COUNTRY OF AUTHOR: ITALY
SOURCE: ACTA OPHTHALMOLOGICA SCANDINAVICA, (SEP 1999) Vol. 77, Supp. [229], pp. 52-52.
Publisher: SCRIPTOR PUBLISHER, SOVANGSVEJ 1-5, DK-2650 HVIDOVRE, DENMARK.
ISSN: 1395-3907.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: CLIN
LANGUAGE: English
REFERENCE COUNT: 5
TI Brimonidine 0.2(behaviour on **intraocular pressure** in **Timolol**-uncontrolled glaucomatous patients
ST Author Keywords: beta-blocker; alpha-adrenoceptor agonist; long-term drift; **glaucoma**
STP KeyWords Plus (R): **AQUEOUS-HUMOR** DYNAMICS; ALPHA-2-ADRENERGIC AGONISTS

L35 ANSWER 174 OF 552 MEDLINE on STN DUPLICATE 31
ACCESSION NUMBER: 2000105853 MEDLINE
DOCUMENT NUMBER: 20105853 PubMed ID: 10641099
TITLE: [Alpha-2 adrenergic agonists in the treatment of **glaucoma**].
Agonistii alfa 2 adrenergici in tratamentul glaucomului.
AUTHOR: Apatachioae I; Chiselita D
SOURCE: OFTALMOLOGIA, (1999) 47 (2) 35-40. Ref: 28
Journal code: 9111247. ISSN: 1120-0875.
PUB. COUNTRY: Romania
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Romanian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000209
Last Updated on STN: 20030204
Entered Medline: 20000203
TI [Alpha-2 adrenergic agonists in the treatment of **glaucoma**].
Agonistii alfa 2 adrenergici in tratamentul glaucomului.
AB The study represent an up-to-date of the role and place of alpha 2-adrenergic agonists in **glaucoma** treatment. The first available alpha 2-agonist, clonidine is of historical importance today. Apraclonidine decrease the **aqueous humor** secretion and episcleral venous pressure. It is employed to prevent or blunt the acute **intraocular pressure** rise after ocular laser therapy.
It is not recommended as long term therapy due to its high incidence of local adverse reactions and tachyphylaxis. Brimonidine became the alpha 2-agonist of choice in **glaucoma** chronic treatment, acting by decreasing **aqueous humor** secretion and increasing uveoscleral outflow. It has a lower incidence of the ocular adverse effects because of greater alpha 2 selectivity. Brimonidine has neuroprotective effect, which is an important feature in the new contexts of **glaucoma** pathogenesis. Brimonidine has hypotensor effect similar with **timolol** but with a greater incidence of adverse local reactions. It has been no effects on cardiopulmonary function. Brimonidine would be. . .

CT . . .
therapeutic use
Clonidine: AE, adverse effects
Clonidine: AA, analogs & derivatives
Clonidine: PD, pharmacology
Clonidine: TU, therapeutic use
English Abstract
***Glaucoma: DT, drug therapy**
Glaucoma: PP, physiopathology
Intraocular Pressure: DE, drug effects
Quinoxalines: AE, adverse effects
Quinoxalines: PD, pharmacology
Quinoxalines: TU, therapeutic use
*Receptors, Adrenergic, alpha-2: AG,. . .

L35 ANSWER 175 OF 552 CAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 32
ACCESSION NUMBER: 1999:115495 CAPLUS
DOCUMENT NUMBER: 130:280147
TITLE: **Aqueous humor** dynamics in .alpha.-chymotrypsin-induced ocular hypertensive rabbits
AUTHOR(S): Melena, Jose; Santafe, Juan; Segarra-Domenech, Jose; Puras, Gustavo
CORPORATE SOURCE: Departamento de Framacologia, Facultad de Farmacia, Universidad del Pais Vasco, Paseo de la Universidad, Vitoria, Spain
SOURCE: Journal of Ocular Pharmacology and Therapeutics (1999), 15(1), 19-27
CODEN: JOPTFU; ISSN: 1080-7683
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **Aqueous humor** dynamics in .alpha.-chymotrypsin-induced ocular hypertensive rabbits

AB Aq. humor dynamics were studied in .alpha.-chymotrypsin-induced ocular hypertensive rabbits either by tonog. or two-level const. pressure perfusion techniques. A significant correlation was obtained between the values of outflow facility in .alpha.-chymotrypsin-induced ocular hypertensive rabbits as detd. by tonog. and const. pressure perfusion. The mean value of tonog. outflow facility in ocular hypertensive rabbits was not statistically different from that found in ocular normotensive rabbits. On the contrary, the estd. rate of aq. inflow in ocular hypertensive rabbits was about 1.5-fold higher than that of ocular normotensive ones. While topical **timolol** lowered **intraocular pressure** and aq. humor inflow in ocular hypertensive rabbits, pilocarpine did not produce any significant effect. Aq. humor protein was significantly increased in ocular hypertensive eyes. The results of this study show that accurate measurements of outflow facility can be obtained in .alpha.-chymotrypsin-induced ocular hypertensive rabbits by tonog. technique. The data suggest that the long-term ocular hypertension induced by .alpha.-chymotrypsin in albino rabbits may be secondary to an increase in the rate of aq. humor inflow, likely produced by a breakdown of the blood-aq. barrier. This finding strongly conflicts with the hypothesis of trabecular blockage as the cause of .alpha.-chymotrypsin-induced ocular hypertension in this species.

ST aq humor chymotrypsin **glaucoma** ocular hypertension

IT **Glaucoma** (disease)
Rabbit
(aq. humor dynamics in .alpha.-chymotrypsin-induced ocular hypertensive rabbits)

IT Disease models
(**glaucoma**; aq. humor dynamics in .alpha.-chymotrypsin-induced ocular hypertensive rabbits)

IT 92-13-7, Pilocarpine **26839-75-8**, **Timolol**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(ocular hypertension induced by .alpha.-chymotrypsin in rabbits sensitivity to)

L35 ANSWER 176 OF 552 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 33
ACCESSION NUMBER: 1999:150148 BIOSIS
DOCUMENT NUMBER: PREV199900150148
TITLE: Prolonged, contemporaneous administration of pilocarpine and **timolol** increases the **aqueous humor** pilocarpine levels in rabbits.
AUTHOR(S): Burgalassi, S.; Chetoni, P. (1); Panichi, L.; Saettone, M. F.
CORPORATE SOURCE: (1) Dep. Pharmaceutical Sci., Lab. Pharmaceutical Technol. Biopharmaceutics, Univ. Pisa, I-56126 Pisa Italy
SOURCE: Journal of Ocular Pharmacology and Therapeutics, (Feb., 1999) Vol. 15, No. 1, pp. 1-7.
ISSN: 1080-7683.
DOCUMENT TYPE: Article
LANGUAGE: English
TI Prolonged, contemporaneous administration of pilocarpine and **timolol** increases the **aqueous humor** pilocarpine levels in rabbits.
AB The purpose of this study was to gather information on the mechanism by which **timolol**/pilocarpine (TI/PI) combination eyedrops provide additive ocular hypotensive effects. An hypothesis, according to which the combination eyedrops prolong the intraocular permanence of PI as a consequence of decreased **aqueous humor** secretion induced by TI, was not supported by clear-cut literature evidence. It was thus sought to verify if repeated instillations. . . PI hydrochloride alone (2% w/v), buffered at pH 5.5 and 6.8, were instilled b.i.d. in albino rabbits for five days. **Aqueous humor** samples, analyzed after the last treatment, showed that the **aqueous humor** PI levels observed after administration of the combination eyedrops were significantly higher than those resulting from administration of the reference. . . with the pH 6.8 reference solution, the pH 5.5 one produced slightly higher and more sustained drug levels in the **aqueous humor**. The present results appear to confirm the assumption that an increased retention of PI in the **aqueous humor** is responsible for the additive effects on **intraocular pressure** reported by several authors for the combination TI/PI eyedrops.
IT Major Concepts
Pharmacology; Sense Organs (Sensory Reception)
IT Diseases
open-angle **glaucoma**: eye disease, treatment
IT Chemicals & Biochemicals
pilocarpine: antiglaucoma - drug, aqueous human levels, contemporaneous administration, prolonged administration; **timolol**: antiglaucoma - drug, contemporaneous administration, prolonged administration
IT Alternate Indexing
Glaucoma, Open-Angle (MeSH)
IT Miscellaneous Descriptors
intraocular pressure
RN 92-13-7 (PILOCARPINE)
26839-75-8 (TIMOLOL)

L35 ANSWER 177 OF 552 USPATFULL on STN
ACCESSION NUMBER: 1998:115761 USPATFULL
TITLE: Prophylactic and therapeutic methods for ocular degenerative diseases and inflammations and histidine compositions therefor
INVENTOR(S): Thomas, Peter G., Charlottesville, VA, United States
PATENT ASSIGNEE(S): Cytos Pharmaceuticals LLC, Durham, NC, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5811446		19980922

APPLICATION INFO.: US 8398054 19970418 (8)
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Kight, John
ASSISTANT EXAMINER: Covington, Raymond
LEGAL REPRESENTATIVE: Angres, Isaac A., Petraglia, Susan P.
NUMBER OF CLAIMS: 45
EXEMPLARY CLAIM: 1
LINE COUNT: 1037
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . vision also arises as a result of ischemia-reperfusion injury that is associated with retinal arterial occlusion, retinal venous occlusion, and **glaucoma**.

SUMM . . . the eye, and especially the cornea. Physical trauma to the cornea may be accompanied by intraocular inflammation, synechiae leading to **glaucoma**, and secondary membrane formation. Collagen is the major structural protein of the cornea. The normal host response to inflammation produces. . .

SUMM Degenerative eye conditions within the purview of the preferred aspects of the invention include, for example, **glaucoma**, diabetic retinopathy, disease-based posterior vitreous detachment (PVD), age-based posterior vitreous detachment (PVD), corneal amyloidosis, age-related macular degeneration, retinal photic injury,. . .

SUMM . . . effectively treat ocular inflammation and its attendant cell damage associated with, for example, one or more diseases or degenerations including **glaucoma**, diabetic retinopathy, disease-based posterior vitreous detachment (PVD), age-based posterior vitreous detachment (PVD), corneal amyloidosis, age-related macular degeneration, retinal photic injury,. . .

SUMM . . . bind collagen (and glycoaminoglycans as well) of the stromal matrix, causing hydration or swelling and shortening of the collagen fibrils. **Glaucoma** is a common sequela of alkali burns, due to a rapid rise in **intraocular pressure** attributable to this shortening of collagen fibrils. The alkali also renders the collagen fibrils more susceptible to enzymatic degradation ("naked. . . cells are not known to contain either latent or active collagenase. Further, if the alkali penetrates the ciliary body, the **aqueous humor** experiences a significant drop in aqueous glucose and ascorbate concentrations. Ascorbate is essential to the biosynthesis of both collagen and. . .

SUMM . . . chromic acid, nitric acid, and acetic acid. Acid burns cause tissue damage by coagulating and precipitating ocular proteins, and secondary **glaucoma** as the result of reacting with collagen (by fibril shortening.) In both alkali and acid burns, the course of therapy. . . usually entails irrigating the eye, followed by administration of one or more of topical antibiotics, topical steroids, collagenase inhibitors, and anti-**glaucoma** agents, oral or topical ascorbate. It is intended that histidine be administered therapeutically following irrigation of the eye injured by. . . 0.3% gentamicin drops or bacitracin ointment), topical steroids (e.g., 1% prednisolone, or 0.1% dexamethasone), collagenase inhibitors (e.g., 10-20% acetyl cysteine), anti-**glaucoma** agents (e.g, 10% phenylephrine) in combination with 2% atropine (a cycloplegic), and oral or topical ascorbate.

SUMM . . . injury, a penetrating injury, or a perforating foreign body which may be accompanied by intraocular inflammation, synechiae which leads to **glaucoma**, and secondary membrane formation. It is equally envisioned that histidine be administered during and after suturing to reduce the inflammation.. . .

SUMM . . . cycloplegic exemplified by atropine; a moitic exemplified by physostigmine, pilocarpine, and carbachol; an antiglaucoma agents exemplified by phenylephrine, acetazolamide, and **timolol** maleate; a collagenase inhibitor exmeplified by acetyl cysteine; a glycoprotein such as fibronectin and vitronectin, as well as analogs or. . .

DETD The following combination therapy as an ophthalmic solution is intended to reduce inflammation and **intraocular pressure** following photoablation of the cornea to improve wound healing:

DETD . . . eye drops (5.0 wt. % histidine, 2-4 drops, 4 times daily) oral

acetazolamide (250 mg, 4 times daily) (for secondary **glaucoma** therapy) is suitable for alkali burns.

CLM What is claimed is:

2. The method according to claim 1 wherein said degenerative eye condition comprises **glaucoma**, diabetic retinopathy, disease-based posterior vitreous detachment (PVD), age-based posterior vitreous detachment (PVD), corneal amyloidosis, age-related macular degeneration, retinal photic injury,. . .

6. The method according to claim 5 wherein said degenerative eye condition comprises **glaucoma**, diabetic retinopathy, disease-based posterior vitreous detachment (PVD), age-based posterior vitreous detachment (PVD), Dellen, Terrein's Marginal Degeneration, or calcific band keratopathy.

. . .

. . . antiviral agent, a corticosteroid, an hydroxyacid, a ketoacid, a non-steroidal antiinflammatory agent, a cycloplegic, a miotic, a collagenase inhibitor, an anti-**glaucoma** agent, a carbonic anhydrase inhibitor, a glycoprotein, and silver nitrate.

. . . amantadine, rimantadine, dexamethasone, prednisolone, prednisone, fluorometholone, betamethasone, hydrocortisone, ketorolac, indomethacin, flurbiprofen, ketoprofen, loxoprofen, diclofenac, atropine, pilocarpine, carbachol, physostigmine, phenylephrine, acetazolamide, **timolol** maleate, fibronectin and vitronectin as well as analogs or fragments thereof, and acetyl cysteine.

. . . antioxidant, an antiviral, a corticosteroid, an hydroxyacid, a ketoacid, a non-steroidal antiinflammatory, a cycloplegic, a miotic, a collagenase inhibitor, an anti-**glaucoma** agent, a carbonic anhydrase inhibitor, a glycoprotein, and silver nitrate.

. . . amantadine, rimantadine, dexamethasone, prednisolone, prednisone, fluorometholone, betamethasone, hydrocortisone, ketorolac, indomethacin, flurbiprofen, ketoprofen, loxoprofen, diclofenac, atropine, pilocarpine, carbachol, physostigmine, phenylephrine, acetazolamide, **timolol** maleate, fibronectin and vitronectin as well as analogs or fragments thereof, and acetyl cysteine.

. . . hydrocortisone, an .alpha.-hydroxyacid, a .beta.-hydroxyacid, an .alpha.-ketoacid, a .beta.-ketoacid, ketorolac, indomethacin, flurbiprofen, loxoprofen, diclofenac, atropine, pilocarpine, carbachol, physostigmine, phenylephrine, acetazolamide, **timolol** maleate, fibronectin and vitronectin as well as analogs or fragments thereof, acetyl cysteine, or mixtures thereof.

L35 ANSWER 178 OF 552 USPATFULL on STN
ACCESSION NUMBER: 1998:115758 USPATFULL
TITLE: Combinations of prostaglandins and clonidine derivatives for the treatment of **glaucoma**
INVENTOR(S): DeSantis, Jr., Louis, Fort Worth, TX, United States
Sallee, Verney L., Southlake, TX, United States
PATENT ASSIGNEE(S): Alcon Laboratories, Inc., Fort Worth, TX, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5811443		19980922
APPLICATION INFO.:	US 8036675		19970221 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. 571326, filed on 12 Dec 1995, now patented, Pat. No. 5605922 which is a continuation of Ser. No. 422570, filed on 10 Apr 1995, now patented, Pat. No. 5480900 which is a continuation of Ser. No. 213380, filed on 14 Mar 1994, now abandoned which is a continuation of Ser. No. 960065, filed on 13 Oct 1992, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Fay, Zohreh

LEGAL REPRESENTATIVE: Copeland, Barry L.
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
LINE COUNT: 500
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Combinations of prostaglandins and clonidine derivatives for the treatment of **glaucoma**

AB Combinations of at least one clonidine derivative and at least one prostaglandin are used to treat **glaucoma** and ocular hypertension without some of the side effects typically associated with topical administration of prostaglandins.

SUMM The present invention relates generally to the field of ophthalmology. In particular, the invention relates to the treatment of **glaucoma** and ocular hypertension using a combination of at least one clonidine derivative (e.g., para-amino clonidine) and at least one prostaglandin.

SUMM Although the underlying causes of **glaucoma** are not understood, its symptoms often include elevated **intraocular pressure**, which may be caused either by over-production of **aqueous humor** or by inadequate outflow of **aqueous humor**. If left untreated, or if inadequately treated, **glaucoma** can lead to blindness or significant loss of vision. There is therefore a continuing need for therapies which control the elevated **intraocular pressure** associated with **glaucoma**.

SUMM There are currently a number of drugs utilized in the treatment of **glaucoma**, including: miotics (e.g., pilocarpine, carbachol and acetylcholinesterase inhibitors); sympathomimetics (e.g., epinephrine and dipivalylepinephrine); alpha-2 agonists (e.g., para-amino clonidine); beta-blockers (e.g., betaxolol, levobunolol and **timolol**); and carbonic anhydrase inhibitors (e.g., acetazolamide, methazolamide and ethoxzolamide). Miotics and sympathomimetics are believed to lower IOP by increasing the outflow of **aqueous humor** through the trabecular meshwork, while beta-blockers, alpha-2 agonists and carbonic anhydrase inhibitors are believed to lower IOP by decreasing the formation of **aqueous humor**.

SUMM In addition, although they have not yet been approved for anti-**glaucoma** therapy, certain classes of prostaglandins and prostaglandin analogues (hereinafter collectively referred to as "prostaglandins") have been shown in various animal models and in some clinical studies to reduce **intraocular pressure** (IOP) to a greater extent than most currently used therapeutic agents. See, for example: U.S. Pat. No. 4,097,489 (Bundy), U.S.. . . et al.). In contrast to the case with miotics, prostaglandins are believed to lower IOP by increasing the outflow of **aqueous humor** via the uveo-scleral route. In addition, prostaglandins may possibly have other effects in the eye, such as enhancing vascular support. . .

SUMM . . . can also cause serious side effects which affect patient compliance and/or necessitate the withdrawal of treatment; at least one beta-blocker, **timolol**, has increasingly become associated with serious pulmonary side effects attributable to its effect on beta-2 receptors in pulmonary tissue; and. . . day. Patient compliance with such complicated dosage regimens can be very poor, particularly in elderly patients. Since the majority of **glaucoma** patients are elderly, this patient compliance problem is significant.

SUMM In light of the foregoing circumstances, it is clear that a need exists for new, more potent anti-**glaucoma** compositions which avoid or reduce the above-cited side effects, while increasing patient compliance. The present invention is directed to such. . .

SUMM . . . been found that administration of one or more prostaglandins in combination with one or more clonidine derivatives controls or lowers **intraocular pressure** (IOP) without the accompanying inflammatory response (including hyperemia) typically found with prostaglandins. The present invention therefore provides compositions and methods useful for the treatment of **glaucoma** and ocular hypertension. The compositions contain a combination of at least one clonidine derivative and at least one prostaglandin which. . .

DETD The present invention utilizes combinations of at least one clonidine

derivative and at least one prostaglandin to treat **glaucoma** and ocular hypertension.

DETD . . . of this compound are incorporated herein by reference. It is also known that certain clonidine derivatives are effective in lowering **intraocular pressure** when applied topically to the eye; this discovery is described in U.S. Pat. No. 4,461,904 (York, Jr.), the entire contents. . .

DETD . . . and their pharmaceutically acceptable esters and salts (hereinafter collectively referred to as "prostaglandins" or "PG's"), which are capable of reducing **intraocular pressure** when applied topically to the eye. Such prostaglandins include the natural compounds: PGE.sub.1, PGE.sub.2, PGE.sub.3, PGF.sub.1.alpha., PGF.sub.2.alpha., PGF.sub.3.alpha., PGD.sub.2 and. . .

DETD The present invention is also directed to methods of treating **glaucoma** and other ophthalmic diseases and abnormalities. The methods comprise topically applying to the affected eye(s) of the patient a therapeutically. . .

CLM What is claimed is:

1. A topical ophthalmic composition for the treatment of **glaucoma**, comprising a combination of a pharmaceutically effective amount of at least one prostaglandin and a pharmaceutically effective amount of at. . .

8. A method of treating **glaucoma**, comprising applying to an affected eye a pharmaceutically effective amount of at least one prostaglandin and a pharmaceutically effective amount. . .

=> d his

(FILE 'HOME' ENTERED AT 18:29:32 ON 27 JUL 2003)

FILE 'REGISTRY' ENTERED AT 18:29:44 ON 27 JUL 2003

```
L1             1 S TIMOLOL/CN
L2             1 S AMILORIDE/CN
L3             0 S ETHYL ISOPROPYL AMILORIDE
L4             0 S ISOPROPYL ETHYL AMILORIDE
L5           131 S AMILORIDE
L6             4 S ETHYL AMILORIDE
L7             1 S CARIPORIDE/CN
```

FILE 'ADISCTI, ADISINSIGHT, ADISNEWS, BIOSIS, CANCERLIT, CAPLUS, CEN, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL, EMBASE, ESBIOBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDICONF, MEDLINE, NAPRALERT, NLDB, NUTRACEUT, PASCAL, PCTGEN, ...' ENTERED AT 18:33:21 ON 27 JUL 2003

```
L8         31558 S L1 OR TIMOLOL
L9         64288 S L2 OR AMILORIDE
L10          507 S L7 OR ACRIPORIDE
L11         1505 S L7 OR CARIPORIDE
L12        95722 S L8 OR L9 OR L11
L13       159500 S GLAUCOMA
L14        34931 S AQUEOUS HUMOR
L15            0 S S ANTIPORT (S) MODULAT?
L16          457 S ANTIPORT (S) MODULAT?
L17          923 S ANTIPORT? (S) MODULAT?
L18         9965 S L12 AND L13
L19           13 S L18 AND L17
L20           10 DUP REM L19 (3 DUPLICATES REMOVED)
L21        82563 S INTRAOCULAR PRESSURE
L22         5371 S L18 AND L21
L23          730 S L14 AND L22
L24         3138 S SODIUM PROTON (S) EXCHANGE
L25            0 S L24 AND L23
L26            0 S AE-2 ANTIPORT
L27            3 S NHE-1 ANTIPORT
L28            3 S NHE ANTIPORT
L29          206 S NHE (S) ANTIPORT
L30           30 S AE2 (S) ANTIPORT
L31            4 S L29 AND L30
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L32           1 S L31 AND L23
L33         232 S L29 OR L30
L34           1 S L23 AND L33
L35         552 DUP REM L23 (178 DUPLICATES REMOVED)

=> s l11 and l13
 95% OF LIMIT FOR L#S REACHED
L36           9 L11 AND L13

=> dup rem
ENTER L# LIST OR (END):l36
DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, DGENE, DRUGLAUNCH,
DRUGMONOG2, KOSMET, MEDICONF, NUTRACEUT, PCTGEN, PHARMAML'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L36
L37           4 DUP REM L36 (5 DUPLICATES REMOVED)

=> d l37 1-4 ibib, kwic

L37  ANSWER 1 OF 4  USPATFULL on STN
ACCESSION NUMBER:        2003:120743  USPATFULL
TITLE:                   Novel combination therapy to treat glaucoma
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                              NUMBER         KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 2003083227      A1   20030501
APPLICATION INFO.:       US 2002-217755     A1   20020813  (10)
RELATED APPLN. INFO.:    Continuation-in-part of Ser. No. US 2002-9581, filed on
                         30 Apr 2002, PENDING

                               NUMBER         DATE
                         ------------------ --------
PRIORITY INFORMATION:    US 1999-133180P    19990507 (60)
                         US 2001-312036P    20010813 (60)
DOCUMENT TYPE:           Utility
FILE SEGMENT:            APPLICATION
LEGAL REPRESENTATIVE:    Evelyn H. McConathy, Esquire, Dilworth Paxson LLP, 3200
                         Mellon Bank Center, 1735 Market Street, Philadelphia,
                         PA, 19103
NUMBER OF CLAIMS:        31
EXEMPLARY CLAIM:         1
NUMBER OF DRAWINGS:      6 Drawing Page(s)
LINE COUNT:              1250
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI     Novel combination therapy to treat glaucoma
SUMM   . . . The present invention relates to the field of ophthalmology. In
       particular, the invention relates to the prevention and treatment of
       glaucoma and associated elevations of intraocular pressure.
SUMM   . . . the world, currently affecting an estimated three million
       people in the United States, with 300,000 new cases diagnosed every
       year. Glaucoma results from obstructed outflow from the
       aqueous humor of the eye, resulting in elevated intraocular pressure in
       the anterior chamber,. . . can also be caused by other conditions,
       such as impaired intraocular fluid transport caused by eye surgery,
       including surgery for glaucoma. The IOP, itself, reflects a
       balance between the rates of inflow (fluid formation) and outflow (fluid
       return) of the aqueous humor by re-absorption. Medical approaches to
       treating glaucoma are frequently directed at reducing the rate
       of net formation of aqueous humor.
SUMM   . . . Ophthalmol. Vis. Sci. 17:958-981 (1978); Walker et al., 1999;
       Wolosin et al., In: The Eye's Aqueous Humor: From Secretion to
       Glaucoma, Civan (ed), Academic Press, Boston, pp 135-162
       (1998)).
SUMM   . . . use of systemic and topical drugs for lowering intraocular
```

pressure. At the present time, medical control of intraocular pressure and **glaucoma** consists of topical, oral or intravitreous administration of many compounds. See generally, Horlington, U.S. Pat. No. 4,425,346; Komuro et al.,. . .

SUMM [0015] Among the most effective medical therapies for **glaucoma** are strategies aimed at reducing intraocular pressure by reducing the net rate of aqueous humor formation by the ocular ciliary epithelial bilayer (see generally, Shields, Textbook of **Glaucoma**, 3rd Ed., Williams & Wilkins, Baltimore (1992)). This can occur either by blocking unidirectional secretion from stroma to the aqueous. . .

SUMM [0016] Four primary classes of drugs are used to treat **glaucoma** . These include: miotics (e.g., pilocarpine, carbachol and acetylcholinesterase inhibitors); sympathomimetics (e.g., epinephrine, metipranolol, dipivefrin, carbachol, dipivalyl, and parn-aminoclonidine); beta-blockers (e.g.,. . .

SUMM . . . than normal intraocular pressure can also be problematic, caused for example, by a variety of conditions, such as surgery for **glaucoma**, retinal detachment, uveitis, and the like. However, since no drugs are presently available for the safe and effective prevention, modulation. . .

SUMM . . . level, although primarily the invention will be useful to relieve or prevent elevated levels of intraocular fluid in, for example, **glaucoma** patients, before vision is adversely and permanently affected. In addition, the present combined therapeutic methods permit known compounds to be. . .

DETD [0031] The methods and compositions of the present invention are intended for treatment of **glaucoma** and other conditions, which manifest elevated intraocular pressure in the eye of a patient, particularly human patients, but also including other mammalian hosts. **Glaucoma** is a term which embraces a group of ocular diseases characterized by elevated intraocular pressure levels which can damage the eye, and destroy the optic nerve and related ganglia. In addition, normotensive **glaucoma** is characterized by an apparent nonelevated intraocular pressure. However, for the patient suffering from normotensive **glaucoma**, the apparently normal pressure is sufficiently high for that particular patient as to cause the same types of nerve and. . .

DETD . . . antiports provide the dominant entry pathway under physiological conditions, and further suggested that carbonic anhydrase inhibitors (commonly used to treat **glaucoma**) act by blocking Na.sup.+/H.sup.+ exchange. More recently an electron-probe X-ray microanalysis (McLaughlin et al., Am. J. Physiol. Cell Physiol. 281:C865-C875(2001)). . .

DETD . . . and it is desirable that such elevated pressures be lowered to below 18 mm Hg. In the case of low-tension **glaucoma**, it is desirable for the intraocular pressure to be lowered below that exhibited by the patient prior to treatment. Intraocular. . .

DETD . . . generally considered below about 8 mm Hg. Such conditions may result from a variety of causes, such as surgery for **glaucoma**, retinal detachment, uveitis, and the like.

DETD [0048] The exemplified inhibitors described in detail in the Examples include **cariporide**, EIPA (ethylisopropylamiloride), DMA (dimethylamiloride) and amiloride, at concentrations characteristic of the NHE-1 isoform. Nevertheless, applicable compounds would include any of. . . such as timolol), or amiloride analogs, as well as, but not limited to, the many compounds produced by Hoechst, i.e., **cariporide**, as well as other compounds that would be recognized as modulators of Na.sup.+ uptake or the anion exchange system. See,. . .

DETD . . . composition, which can include drugs, compounds, pharmaceuticals or the like, can be used to treat an individual, such as a **glaucoma** patient.

DETD . . . and Cl.sup.-/HCO.sub.3.sup.- antiports) and the effect of blocking both, also explains the clinical efficacy of carbonic anhydrase inhibitors in treating **glaucoma**. Reducing the availability of H.sup.+ and HCO.sub.3.sup.- to both antiports, thereby synergistically inhibits the initial step in aqueous humor secretion.. . . this step could be selectively blocked in glaucomatous patients by specifically inhibiting NHE-1 with low concentrations of EIPA, DMA or